REMARKS

Upon entry of the above amendment, claims 13-36, 38, 42, 43, and 49-66 will be pending in the case, claims 44-48 having been newly canceled and new claims 54-66 added. Claim 38 is amended to correct its dependency. The amendments to independent claims 13, 35, 36, 42 and 43 incorporate the limitations of claims 44-48 and also amend the preamble language to correspond to the language in the bodies of those claims. Support for new claims 54-57 can be found throughout the application, e.g., at page 2, lines 8-20 (note that "bid" means twice per day); page 3, lines 9-14; page 4, lines 19-23; and page 8, lines 24-29. New claims 58-66 are supported, e.g., at page 8, lines 24-25; and at page 9, lines 5-6. No new matter has been added.

All of the claims pending prior to this amendment were rejected on one or more grounds, as discussed below.

Rejection under 35 USC § 101

Claims 13-36, 38, 42, and 43 were rejected as allegedly being directed to non-statutory subject matter, with the Office taking the position that the claimed methods do not effect a "transformation" and that a "transformation" is essential for statutory subject matter. Applicant continues to disagree with the Office's position, for the reasons articulated at pages 10-11 of Applicant's Reply filed 21 December 2009. In that Reply, Applicant pointed out, *inter alia,* that a "transformation" does occur when a patient is transformed into someone with an inhaler and recommendations for use of the inhaler, as in the presently claimed methods. Applicant also explained that "transformation" is but one of two alternate tests for statutory subject matter of a process claim promulgated by the Federal Circuit's *en banc* opinion in *In re Bilski*, the other test being the so-called "machine or apparatus" test, and that the present claims unquestionably meet the "machine or apparatus" test. The present Office action does not even address the latter portion of Applicant's arguments, much less attempt to refute it.

Claims 44-53 were not rejected under § 101, an implicit acknowledgement that each of claims 44-53 is directed to statutory subject matter. In an effort to further prosecution, Applicant has amended each of the independent claims (i.e., claims 13, 35, 36, 42, and 43) to incorporate

the limitations of claims 44-48, respectively. This amendment moots the rejection as to all of claims 13-36, 38, 42, and 43. Withdrawal of the rejection under § 101 is therefore respectfully requested.

Rejection under 35 USC § 112, paragraph two

Claims 13-36, 38, and 42-53 were rejected as being indefinite because, according to the Office action at pages 7-8, the preamble recites a method of "prevention and/or treatment," while the steps of the claim do not require that the composition actually be inhaled by the patient. Applicant disagrees that this renders the claimed method indefinite, as it is clear from the steps of the claim what method is being claimed. However, in an effort to further prosecution, Applicant has amended the preambles of the independent claims to read: "A method of providing an inhaler to an asthma patient… ." Withdrawal of the rejection is therefore respectfully requested.

Rejections under 35 USC § 103(a)

As in previous Office actions, the present Office action dated 17 March 2010 asserts that claims 13-15, 17, 18, 20-36, 38, and 42-53 are obvious over Carling, and that the remaining claims (claims 16 and 19) are obvious over a combination of Carling, Aberg et al. and Ryrfeldt et al. Carling is the primary reference. Aberg et al. and Ryrfeldt et al. are cited solely for their alleged disclosure of the (R,R) isomer of formoterol and the 22R epimer of budesonide, respectively. To the extent that the rejections may be applied to the claims as presently amended, Applicant again traverses.

The rationale for the rejection is set out on pages 3-5 and 8-12 of the present Office action. As it is essentially the same as the rationale stated in prior Office actions (e.g., those dated 4 December 2007, 6 October 2008, and 25 June 2009), Applicant begins by reaffirming the arguments provided at pages 19-37 of Applicant's Reply filed 3 June 2008 and elaborated at pages 11-16 of the Reply filed 3 April 2009 and pages 11-13 of the Reply filed 21 December 2009. Rather than repeat those arguments here, Applicant simply incorporates them by reference into the present Reply and focuses instead on just a few of the points made on

pages 3-5 of the present Office action, plus some additional evidence of nonobviousness newly presented below.

> According to the present Office action at page 3,
>
> Applicant argues that Applicant has previously pointed out that Carling says the combination should be administered just twice per day (BID) and that the Examiner has acknowledged. The examiner is in agreement with Carling's teaching of BID dosing, however, the Examiner has also pointed out previously that Carling et al. on pages 7-9 exemplify amounts of active agents per dose of inhalation, which calculate up to 8 inhalation per day without going over the maximum daily dosage in the treatment of asthma. Therefore, one of ordinary skill in the art would immediately [recognize] that a patient experiencing acute asthmatic attack even with ongoing twice a day dosing regimen, he still can safely inhale additional 6 inhalations without going over the maximum suitable daily dosage in general asthmatic condition taught by Carling et al. to achieve its known therapeutic relief from asthmatic attack. (Informal English in the original)

The above passage indicates that the Examiner agrees with Applicant that Carling et al. teaches that the formoterol/budesonide combination should be administered BID, i.e., just twice per day. The Examiner, however, has interpreted Carling et al.'s teaching of an exemplary unit dose of the combination as containing 12 μg formoterol, combined with Carling et al.'s teaching that a "suitable daily dose of formoterol is in the range of 6 to 100 μg," as meaning that all patients can "safely inhale additional 6 inhalations" and that all patients can decide for themselves when and whether to take some or all of those additional 6 inhalations of the composition on any given day. Applicant submits that this is a fundamental misreading of Carling et al. Carling et al. preceded the statement about a "suitable daily dose of formoterol" by saying "The intended dose regimen is a twice daily administration." Thus, Carling et al. envisioned the patient as being given a prescription that sets a particular, set, invariant daily dose of the combination containing an amount of formoterol between 6 to 100 μg, and being told to inhale half of the set daily dose in the morning and half in the evening. If the unit dose of formoterol delivered by the inhaler is, say, 12 μg, and the patient is told to administer a total of 96 μg per day, then the patient would be instructed to inhale four "puffs" in each morning administration, and four more "puffs" in a second administration in the evening. Under no circumstances is it left to the patient to decide what total dose to inhale on a given day, and in how many separate administrations over the course of the day. Further, the fact that Carling et al. said that a "suitable daily dose of

formoterol is in the range of 6 to 100 μg" does not mean that all doses within this range would be suitable for all patients. It simply means that, for any given patient, a dose suitable for that patient will likely like somewhere within that range. As taught by Carling et al. at page 6, lines 27-29, "The particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc)." Thus, a physician would know not to prescribe a set daily dose at the high end of the range for children or for relatively small patients, or for patients whose disease is relatively mild.

The Examiner may be confusing the sort of treatment taught by Carling et al. (i.e., regular, twice-daily maintenance treatment, traditionally with a steroid or a long-acting bronchodilator, given every day regardless of the patient's symptoms or lack of symptoms on that day) with an entirely different sort of treatment, traditionally with a short-acting β2-agonist bronchodilator, such as terbutaline, designed to give rapid, emergency relief for an acute asthma attack. The latter type of bronchodilator is what a physician would have told a patient to use on an as-needed basis to relieve acute attacks, and certainly not a composition containing a steroid such as budesonide and a long-acting bronchodilator such as formoterol. There is no basis in Carling et al., or anywhere else in the art, for the Examiner's assertion that it would have been "obvious" for a clinician to instruct the patient to freely use the formoterol/budesonide composition "to self-medicate at the time of exacerbation of unexpected asthmatic attack when needed as determined by the patient with out going over the daily safe and effective amounts taught by Carling." Though Carling et al. does use the term "rescue medicine" at page 4, line 8, the context of this phrase shows that Carling et al. was simply describing the rapid onset of action of formoterol (a long-acting β2 agonist) when used in a twice-per-day maintenance regimen, compared to the slower onset of other long-acting β-agonists such as salmeterol. There is no suggestion in Carling et al. that the budesonide/ formoterol combination should be taken more than twice per day, and certainly no suggestion that it be taken "as needed" or for relief during an acute asthma attack in the same manner as a short-acting β2 agonist such as terbutaline. In fact, the sentence at the end of the paragraph that mentions "rescue medicine" clearly states how the budesonide/formoterol combination should be used: "**The combination according to the present invention permits a twice daily dosing regime as a basic treatment of asthma, including nocturnal asthma.**" (emphasis added) One of ordinary skill in the art

would understand Carling et al. to have intended that the combination be administered in precisely the daily amount prescribed by the physician, no more and no less, and that the daily amount should be divided into exactly two administrations each day—presumably one in the morning and one in the evening.

In contrast to the utter lack of evidence provided by the Examiner to support her assertions, Applicant has submitted extensive evidence that one of ordinary skill would NOT have instructed the patient to inhale the Carling et al. composition "as needed" or during an acute asthma attack or in any context other than the prescribed twice-per-day fixed dose, and that a patient would NOT have inhaled further doses of the composition (beyond the prescribed twice-per-day maintenance doses) without consulting with the physician, whether during an asthma attack or not. The present Office action fails to address Applicant's prior filed evidence at all, much less explain why it is not persuasive. Applicant therefore summarizes it again here and asks the Examiner to give it due consideration.

One such item of evidence previously submitted by Applicant is the prior art Pulmicort Turbuhaler® budesonide product insert that is Exhibit A filed with Applicant's Brief on Appeal submitted 3 March 2006 in an appeal to the Board of Patent Appeals and Interferences in this case (hereinafter the "Appeal Brief"). Applicant submitted this product insert to illustrate that those of ordinary skill in the art at the priority date knew that budesonide should be administered no more than twice per day, and certainly not "as needed". (See the discussion of this Exhibit A in the Appeal Brief and again in Applicant's Reply filed 3 June 2008, and note, for example, the sections of Exhibit A hand-labeled "G","C", and "F", respectively: **"Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of PULMICORT TURBUHALER in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose…. The patient should not alter the prescribed dosage unless advised to do so by the physician…. If symptoms do not improve in that time frame, or if the condition worsens, the patient should be instructed to contact the physician…. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur (see PRECAUTIONS)."**) These instructions stem from the fact that budesonide is a corticosteroid, and like other drugs of that class can induce dangerous side

effects such as hypercorticism in patients. Thus, the physician is cautioned to prescribe the "lowest effective dose" for administration on a regular basis, twice per day, and to warn the patient not to take a larger dose than prescribed. See also the text of Exhibit A immediately above the section labeled "I" on page 2: **"This medicine is NOT intended to provide rapid relief of your breathing difficulties during an asthma attack. It must be taken at regular intervals as recommended by your doctor, and not as an emergency measure."** Applicant submits that this *taught away* from the presently claimed methods. As the Examiner is no doubt aware, the seminal Supreme Court case *United States v. Adams*, 383 U.S. 39 (1966), firmly established the concept that a *teaching away* in the art is evidence of nonobviousness: "Known disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness." Long after the holding in *Adams*, the Court of Appeals of the Federal Circuit described the standard for a *teaching away* as follows: "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 989 (Fed. Cir. 2006). Note also the holding in *Takeda Chemical Industries, LTD. v. Alphapharm PTY., LTD.*, 492 F.3d 1350, 1358-9 (Fed. Cir. 2007), which relied heavily on the *teaching-away* in a published article regarding the negative side effects of a prior art compound ("compound b") in finding that it would not have been obvious to select compound b and modify it to end up with the claimed compound, pioglitazone.

In the present case, the prior art Pulmicort Turbuhaler® product insert taught one of ordinary skill that this budesonide-containing product should not be inhaled more than twice per day, never "as needed," and never altering the dose without a physician's specific instruction. These warnings, which stem at least in part from the recognized dangers of overdosing on corticosteroids, are consistent with Carling et al.'s teachings that the budesonide/formoterol combination should be inhaled just twice per day: "a twice daily dosing regime as a basic treatment of asthma" (Carling et al. at page 4, lines 20-21); "the intended dose regimen is a twice daily administration" (Carling et al. at page 6, lines 22-23). Since the prior art of record consistently led one of ordinary skill "in a direction divergent from the path that was taken by the applicant," it meets the Federal Circuit's standard for a *teaching away* from the claimed methods,

as set out in *Optivus Tech. v. Ion Beam Applications*. Accordingly, one of ordinary skill in the art would have had neither a motivation to carry out the presently claimed methods nor a reasonable expectation of success upon doing so. Applicant respectfully requests that the Examiner acknowledge that the teachings of the budesonide product insert constitute a *teaching-away* from the presently claimed methods, or explain why she believes otherwise.

A second product insert that was cited in the Appeal Brief and has been discussed repeatedly in the Office actions and Replies since then is the Symbicort® Turbuhaler® budesonide/formoterol fumarate dihydrate product insert submitted as Exhibit B in the Appeal Brief. Exhibit B describes use of the Symbicort® product in a twice-per-day maintenance dosing regimen (similar to the dosing regimen for the Pulmicort® budesonide-only product that is the subject of the Exhibit A product insert discussed above). The Appeal Brief pointed to a number of passages from Exhibit B that support the nonobviousness of the presently claimed methods. Two of these, hand-labeled "D" and "E" on page 2 of Exhibit B, together read as follows: "**If patients find the treatment ineffective, or exceed the current dose of the fixed combination, medical attention must be sought. Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy.**" This warning to seek medical attention if the prescribed twice-per-day dose of the combination is exceeded on a given day illustrates what those of ordinary skill in the art even years after Carling et al. was published understood about the budesonide/formoterol combination: that it should be used as a maintenance treatment twice per day at a fixed dose set by the physician (just as taught by Carling et al.), with no option for additional doses over the course of the day—indeed, any such additional doses were strictly prohibited. Instead, the patient was given a different drug, a short-acting β2 agonist bronchodilator such as terbutaline (i.e., the "rescue bronchodilators" referred to in the second quoted sentence), to use whenever his or her symptoms worsened during the day. Though the Examiner appears to believe it would have been "obvious" to tell the patient to take more doses of Carling et al.'s budesonide/formoterol combination when symptoms worsen, the fact is that the art even years after Carling et al.'s publication date warned that more doses should never be taken. The Office action opines at page 5 that it would be obvious to instruct a patient "to self-medicate at the time of exacerbation of unexpected asthmatic attack when needed as determined by the patient." In

reality, the patient would have been instructed to self-medicate in such an emergency situation with the patient's short-acting β2 agonist inhaler, designed to provide immediate relief, and not the budesonide/formoterol maintenance inhaler, designed to provide long-term bronchodilation and anti-inflammatory effects. Applicant reminds the Examiner that, prior to the present invention, inhaled glucocorticosteroids were never prescribed for use in an acute situation, since glucocorticosteroids are not bronchodilators, were understood to be slow-acting and ineffective for relieving acute attacks, and present a significant risk of steroid overdosing if taken in a dosage that exceeds the fixed amount prescribed by the physician. See, for example, the statements in Exhibit A of the Appeal Brief (the Pulmicort Turbuhaler product insert) labeled D and E:

> **PULMICORT TURBUHALER is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measure are required…. PULMICORT TURBUHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma.**

See also the third column of the "Patient's Instructions for Use" on page 2 of Exhibit A, which says, *inter alia*,

> **DO NOT inhale more doses or use your Turbuhaler more often than instructed by your doctor. This medicine is NOT intended to provide rapid relief of your breathing difficulties during an asthma attack. It must be taken at regular intervals as recommended by your doctor, and not as an emergency measure.** (Emphasis in the original)

In addition to the above evidence of how one of ordinary skill in the art would have viewed budesonide-containing products, including a budesonide/formoterol combination, Applicant has previously provided several lines of evidence that use of the budesonide/formoterol combination as both a maintenance treatment and as a reliever medication inhaled as needed, as determined by the patient, provides dramatically surprising results when directly compared to use of the same combination in accordance with Carling et al.'s teachings, i.e., for twice-daily maintenance treatment alone (presumably with a separate, short-acting β2 agonist bronchodilator employed as-needed, as would be typical). Applicant asks that the Examiner reconsider the surprising results described in Exhibit D submitted with the Appeal Brief (i.e., O'Byrne et al., Am J Respir Crit Care Med 171:129-136 (2005)) and summarized in

the Appeal Brief at pages 27-28. O'Byrne et al.[1] compared one group of patients taking the budesonide/formoterol combination for twice-per-day maintenance treatment (i.e., in accordance with Carling et al.'s teachings) and using a separate, short-acting β2 agonist (terbutaline) as-needed for relief of asthma symptoms, with a second group relying on the budesonide/formoterol combination both for twice-per-day maintenance treatment and as-needed for relief of symptoms (i.e., in accordance with the present claims). Nothing in Carling et al. could have led one to expect the quite dramatic improvements seen in several measures of efficacy (such as the rate of exacerbations) in the second group of patients. The Examiner is asked to explain why this evidence of multiple surprising results is not dispositive of the question of obviousness, particularly in view of the understanding in the prior art that budesonide and other glucocorticosteroids were not useful for immediate relief of symptoms and should not be administered on an as-needed basis.

New evidence

Applicants submit herewith as Appendices A-E several recently published studies, each providing further evidence of surprising results.

The first is Kuna et al., "Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations," Int J Clin Pract 61:725-736 (2007) (Appendix A). As in O'Byrne et al., the Kuna et al. study showed a dramatic reduction in asthma exacerbations achieved with treatment in accordance with the claimed methods, compared to treatment in accordance with Carling et al.'s twice-per-day maintenance regimen. The new study investigated whether this reduction in exacerbations might be attributable to the fact that patients treated in accordance with the claimed methods ultimately received a higher total daily dose of budesonide/formoterol than those on a maintenance-only regimen. In the Kuna et al. study, one group of patients inhaled a maintenance dose of 160 μg budesonide and 4.5 μg formoterol fumarate dihydrate from an inhaler twice per day, every day, plus additional inhalations of the same combination as needed for relief of asthma attacks, as determined by the patient. That treatment was referred to as "SMART" (short for "Symbicort® Maintenance And Reliever

[1] The O'Byrne et al. study and the Kuna et al., Rabe et al., Bousquet et al., and Scicchitano et al. studies described below were supported by AstraZeneca, the assignee of the present application.

Therapy"). A second group of patients inhaled a maintenance dose of 320 μg budesonide and 9 μg formoterol fumarate dihydrate twice per day (i.e., double the maintenance dose given to the "SMART" group) and used terbutaline (not budesonide/formoterol) as an as-needed reliever medication. The patients in that second group, referred to by Kuna et al. as the "budesonide/formoterol" group, received a total of **640 μg budesonide and 18 μg formoterol fumarate dihydrate** per day over the course of the study, compared to the average total of only **483 μg budesonide and 13.6 μg formoterol fumarate dihydrate** per day administered to the patients of the "SMART" group. See Figure 5 on page 733. Despite receiving an overall lower total daily dose of budesonide/formoterol (and no terbutaline at all) compared to the second group, the SMART group suffered far fewer severe exacerbations than did the second group. See Table 2 on page 730, which reports that the SMART group had a total of **125** severe exacerbations (adding up to a total of 692 days of exacerbations) during the study, while the "budesonide/formoterol" group had **173** severe exacerbations, adding up to a total of 1143 days of exacerbations. Thus, even though the SMART group received only 75% of the total daily dose of budesonide/formoterol received by the second group, and were given no terbutaline at all, the rate of severe exacerbations in the SMART group was 28% lower than the rate in the second group. ***Nothing in Carling et al., nor in any other prior art, could have predicted such a counterintuitive result.***

Further surprising results can be found in Rabe et al., "Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomized controlled, double-blind study," Lancet 368:744-753 (2006) (Appendix B). Rabe et al. divided his patients into three groups, all three of which received the same twice-daily maintenance treatment with a budesonide/formoterol combination inhaler, but different reliever therapies for as-needed use: one group used budesonide/formoterol as the reliever (as well as for maintenance treatment), the second used formoterol as the reliever, and the third used terbutaline as the reliever. Consistent with O'Byrne et al.'s results, Rabe et al. found a much lower rate of exacerbations in patients who used the budesonide/formoterol combination both for maintenance and for as-need relief, compared to patients in the third group who used the combination solely for maintenance and used terbutaline for as-needed relief. See Table 2 on page 748 of Rabe et al. The same Table 2 also shows that using the budesonide/formoterol combination as a reliever was

superior to using formoterol alone as the reliever, illustrating that the benefit of the combination when used as a reliever is not entirely attributable to the formoterol component of the combination. (Since formoterol is a bronchodilator and budesonide is not, it would have been reasonable to expect the improvement seen with the combination to be entirely attributable to formoterol.) See also the graph in Figure 2. ***Given the teachings in the art that budesonide and other glucocorticosteroids are of no use as reliever medications because of their lack of bronchodilatory effect and the long time it takes for them to exert their anti-inflammatory effects, it was surprising to find that the budesonide/formoterol combination was superior to formoterol alone as a reliever medication, when each was used in conjunction with budesonide/formoterol maintenance therapy.*** Nothing in the prior art would have predicted this outcome.

More surprising results are reported in the papers enclosed as Appendices C and D. Appendix C is Scicchitano et al., "Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma," Curr Med Res Opin 20(9):1403-1418 (2004). Appendix D is Bousquet et al., "Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone," Resp Med 101:2437-2446 (2007). Each of these studies compared methods in accordance with the present invention to other methods of treating asthma, and found that the presently claimed methods were far superior in reducing the number of exacerbations, as well as by other measures of efficacy, ***even though the patients treated in accordance with the presently claimed methods received a much lower total dose of inhaled corticosteroid.***

Finally, as further objective evidence of nonobviousness, Applicant brings to the Examiner's attention a recent opinion piece attesting to the impact the presently claimed invention has had on asthma therapy: D'Urzo, "Inhaled Glucocorticosteroid and Long-Acting β2-Adrenoceptor Agonist Single-Inhaler Combination for Both Maintenance and Rescue Therapy," Treat Respir Med 5:385-391 (2006) (Appendix E). According to D'Urzo,

> **The use of a single inhaler (budesonide/formoterol) for both maintenance and reliever therapy represent a significant paradigm shift in asthma management that is simple and effective.** (page 389, last paragraph)

D'Urzo refers to this as "**a novel strategy**" (page 390, first full paragraph), and opines:

> **The concept of single-inhaler maintenance and reliever therapy represents one of the most important advances in asthma management in many years, and one that appears particularly well suited for utilization in the primary care setting.** (page 390, last paragraph)

Thus, D'Urzo adds his voice to that of Peter J. Barnes, M.D., who wrote in the editorial submitted as Exhibit E with the Appeal Brief that the O'Byrne et al. results were "**remarkable**" and "**surprisingly good results**" that "**may lead to changes in the paradigm of asthma management**." See the discussion of the Barnes editorial on pages 28-29 of the Appeal Brief. Plainly neither D'Urzo nor Barnes (both experts in the field) viewed use of budesonide/formoterol combination in accordance with the present claims to have been "obvious" in view of standard asthma therapy, i.e., therapy in which a glucocorticosteroid (whether alone or in combination with a second agent) is used solely for maintenance treatment, never as-needed as a reliever.

Summary

Applicant has amended the claims, addressed several points raised in the present Office action, and presented new objective evidence of nonobviousness for the Examiner's consideration. Applicant understands that the above amendments overcome the rejections under 35 USC § 101 and 112, second paragraph. It is believed that the arguments and evidence discussed above, together with arguments and evidence already of record (all of which are incorporated by reference herein), incontrovertibly establish the nonobviousness of the present claims over Carling et al. alone or Carling et al. taken with Aberg et al. and Ryrfeldt et al. Withdrawal of the rejections and allowance of the claims are respectfully requested.

The fee in the amount of $676.00 for excess claim fees is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Apply any other charges or credits to deposit account 06-1050, referencing attorney docket no. 06275-0188001.

Respectfully submitted,

Date: June 16, 2010

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doi: 10.1111/j.1742-1241.2007.01338.x

ORIGINAL PAPER

International Journal of Clinical Practice

Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations

Appendix A

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SUMMARY

This randomised, double-blind, 6-month study compared budesonide/formoterol for maintenance and relief with salmeterol/fluticasone and a fixed maintenance dose of budesonide/formoterol, both with terbutaline for relief. Following a 2-week run-in, 3335 symptomatic adults and adolescents (mean FEV_1 73% predicted, mean inhaled corticosteroid dose 745 μg/day) received budesonide/formoterol 160/4.5 μg one inhalation bid plus additional inhalations as needed, salmeterol/fluticasone 25/125 μg two inhalations bid plus as-needed terbutaline or budesonide/formoterol 320/9 μg one inhalation bid plus as-needed terbutaline. Budesonide/formoterol for maintenance and relief prolonged the time to first severe exacerbation requiring hospitalisation, emergency room treatment or oral steroids (primary variable) vs. fixed-dose salmeterol/fluticasone and budesonide/formoterol ($p = 0.0034$ and $p = 0.023$ respectively; log-rank test). Exacerbation rates were 19, 16 and 12 events/100 patients/6 months for salmeterol/fluticasone, fixed-dose budesonide/formoterol and budesonide/formoterol for maintenance and relief, respectively, [rate reduction vs. fixed-dose salmeterol/fluticasone (0.61; 95% CI 0.49–0.76, $p < 0.001$) and vs. fixed-dose budesonide/formoterol (0.72; 95% CI 0.57–0.90, $p = 0.0048$)]. Budesonide/formoterol maintenance and relief patients used less inhaled corticosteroid vs. salmeterol/fluticasone and fixed-dose budesonide/formoterol patients. All treatments provided similar marked improvements in lung function, asthma control days and asthma-related quality of life. Budesonide/formoterol for maintenance and relief reduces asthma exacerbations and maintains similar daily asthma control at a lower overall drug load compared with fixed-dose salmeterol/fluticasone and budesonide/formoterol.

What's known

Clinical evidence has shown that asthma management using budesonide/formoterol (Symbicort®) maintenance and reliever therapy (SMART) provides a simpler and more effective treatment strategy than traditional approaches with short-acting β_2-agonist (SABA) therapy. SMART improves daily symptom control and prevents severe exacerbations more effectively than higher doses of inhaled corticosteroid (ICS) plus SABA or the same maintenance dose of budesonide/formoterol plus as-needed terbutaline or formoterol. The SMART approach has been recommended in the recent GINA guidelines.

What's new

The evidence within this manuscript confirms that patients randomised to receive SMART therapy have greater protection from severe asthma exacerbations, including hospitalisations and emergency room treatment, than those treated even with higher traditional fixed-dose ICS/long-acting β_2-agonist (LABA) treatment. Similar levels of daily asthma symptom control were observed compared with treatment with salmeterol/fluticasone or fixed-dose budesonide/formoterol. The observed improvements in overall asthma control occurred despite a 50% reduction in regular maintenance doses of ICS/LABA with the SMART approach.

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Disclosures

PK was reimbursed by GlaxoSmithKline, AstraZeneca, Merck, Sharpe & Dohme, Ivax and Boehringer Ingelheim for attending several international conferences in 2004, 2005 and 2006. PK participates as a speaker in scientific meetings and courses organised and financed by various pharmaceutical companies (GlaxoSmithKline, AstraZeneca, Merck, Sharpe & Dohme, Ivax, Boehringer Ingelheim, Altana, Nevitet, Allergopharma, Polpharma, Novartis) and participated in advisory board meetings for GlaxoSmithKline, Merck, Sharpe & Dohme and Boehringer Ingelheim. The institution where PK is employed received a research grant from Merck, Sharpe & Dohme in 2004. MP has received support for travel to

Introduction

The current treatment recommended by guidelines for persistent asthma is a fixed-dose inhaled corticosteroid (ICS) or an ICS/long-acting β_2-agonist (LABA) combination administered twice daily (bid), plus a short-acting β_2-agonist (SABA) as needed for symptom relief. The two ICS/LABA combination inhalers currently available – budesonide/formoterol and salmeterol/fluticasone – are highly effective at providing early and sustained improvements in asthma control for patients symptomatic on ICS alone (1–3).

Even with such treatments, asthma control remains suboptimal (4). Residual asthma symptoms can persist, even in patients using regular ICS or ICS/LABA maintenance therapy, with exacerbations ranging from mild increases in symptoms to events requiring medical intervention or hospitalisation (1,5,6). Consequently, asthma management plans have been developed that specify treatment changes in response to increasing symptoms or deteriorating lung function. These effectively reduce the rate of exacerbations (7), but require detailed physician guidance and patient adherence. Despite strong advocacy and evidence of effectiveness, the use of asthma management plans remains disappointingly low (8).

A new approach to asthma therapy is budesonide/formoterol (Symbicort®) maintenance and reliever therapy (SMART) using one inhaler, without the

international conferences from AstraZeneca and GlaxoSmithKline, and remuneration for serving on advisory boards and speaking at educational meetings for AstraZeneca and GlaxoSmithKline. MP has provided expert witness testimony for AstraZeneca. AM served on the advisory board for AstraZeneca and Merck, Sharpe & Dohme between 2003 and 2004. AM was reimbursed for serving on the AstraZeneca advisory board. AM has been reimbursed for delivering lectures for AstraZeneca, Merck, Sharpe & Dohme and Novartis. CJ and IN are employed by AstraZeneca and hold shares in the company. NEMJ has not declared any conflict of interest. RB has received reimbursement for attending scientific conferences and/or fees for speaking at CME conferences and/or consulting from Altana, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Fujisawa, GlaxoSmithKline, Merck, Sharpe & Dohme, Novartis, Pfizer, Schering Plough and Zambon. The Pulmonary Department at Mainz University Hospital, where RB is employed, received financial compensation for services performed during participation in single- and multi-centre clinical phase I–IV trials organised by various pharmaceutical companies.

requirement for a separate SABA (9–12). This novel treatment approach has also been endorsed in the latest Global Initiative for Asthma (GINA) guidelines (13). The simple substitution of budesonide/formoterol for SABA allows the dose of controller medication, LABA and ICS, to be increased quickly in response to symptoms, while simultaneously offering rapid symptom relief. A previous study has shown that SMART is more effective at reducing exacerbations and improving daily asthma control than the same maintenance dose of budesonide/formoterol plus as-needed SABA (9). In that study, however, SMART patients used, on average, a higher daily dose of budesonide/formoterol than fixed-dose budesonide/formoterol patients. Therefore, a comparison of the efficacy of SMART with that of a higher maintenance dose of ICS/LABA was needed to answer two remaining questions: could SMART be as effective at reducing exacerbations as a higher fixed maintenance dose of combination therapy and would SMART result in greater day-to-day fluctuations in asthma control?

Using a double-blind approach, we hypothesised that SMART (budesonide/formoterol 160/4.5 μg one inhalation bid plus additional as-needed inhalations for relief) would prevent exacerbations more effectively than a fixed dose of salmeterol/fluticasone (25/125 μg two inhalations bid) plus terbutaline or a comparable fixed maintenance dose of budesonide/formoterol (320/9 μg one inhalation bid) plus terbutaline as needed (1,14), and that this important benefit would not be achieved at the expense of daily asthma control.

Methods

In this study (study code SD-039-0735), outpatients aged ≥ 12 years with a diagnosis of asthma [as defined by the American Thoracic Society (15)] for ≥ 6 months and using ICS for ≥ 3 months [≥ 500 μg/day of budesonide or fluticasone (or ≥ 1000 μg/day of another ICS) for ≥ 1 month] were eligible for enrolment. Patients had to have a forced expiratory volume in 1 s (FEV_1) ≥ 50% predicted normal with ≥ 12% reversibility following terbutaline 1 mg and ≥ 1 asthma exacerbation in the previous 1–12 months. Patients using reliever medication on ≥ 5 of the last 7 days of the 2-week run-in were randomised; those with > 10 as-needed inhalations in any day of run-in and patients who experienced an asthma exacerbation during run-in were not randomised. Patients using systemic corticosteroids or with respiratory infections affecting asthma control within 30 days of study entry were excluded.

Study design

This 6-month, randomised, double-blind, double-dummy, parallel-group study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. Independent ethics committees approved the study protocol, patient information and consent forms. All patients and parents/guardians of adolescents gave written informed consent. The first patient was enrolled on 19 December 2003 and the last patient completed the study on 11 March 2005.

Patients attended the clinic at the beginning and end of run-in (visits 1–2), and after 8, 16 and 24 weeks of treatment (visits 3–5 respectively). During run-in, patients used their regular ICS for maintenance and terbutaline (Bricanyl® Turbuhaler®; AstraZeneca, Lund, Sweden) for symptom relief. ICS/LABA combination inhalers were stopped 72 h before study entry and the corresponding ICS dose used. Following run-in, eligible patients were randomised to one of three treatment groups for 24 weeks (Figure 1): budesonide/formoterol (Symbicort® Turbuhaler®; AstraZeneca, Sweden) 160/4.5 μg one inhalation bid for maintenance plus additional inhalations as needed (Symbicort SMART®); fixed-dose salmeterol/fluticasone [Seretide™/Advair™ Evohaler™ (pressurised metered-dose inhaler, pMDI), GlaxoSmithKline, Uxbridge, UK] 25/125 μg two inhalations bid plus terbutaline as reliever medication or budesonide/formoterol 320/9 μg one inhalation bid plus terbutaline. The salmeterol/fluticasone dose, delivered via a dry-powder inhaler (DPI), has been shown in previous studies to have similar clinical efficacy to the fixed dose of budesonide/formoterol used in this study (1,14). In addition, therapeutic equivalence has been reported for salmeterol/fluticasone delivered via either DPI or pMDI (16,17).

At the start of the study, all patients were instructed in the correct use of the Turbuhaler and the Evohaler devices. As an additional safety precaution, any patient who required > 10 inhalations of reliever medication on any 1 day was asked to contact the investigator for reassessment.

Randomisation and blinding

The randomisation schedule was computer-generated at AstraZeneca Research and Development, Charnwood, UK. Within each centre, patients were randomised strictly sequentially as they became eligible. Individual treatment codes and code envelopes (indicating the treatment allocation for each randomised patient) were provided, but code envelopes were to be opened only in case of medical emergencies.

To maintain the blinding, all patients received three inhalers. Patients were instructed to take one

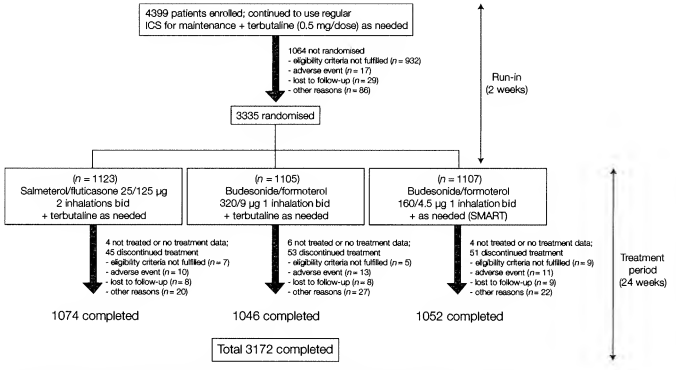

Figure 1 Patient flow. bid, twice daily; ICS, inhaled corticosteroid; SMART, Symbicort® maintenance and reliever therapy. Terbutaline dose expressed as 0.5 mg/inhalation metered dose corresponds to 0.4 mg/inhalation delivered dose

inhalation from the inhaler with the red grip (budesonide/formoterol or placebo Turbuhaler) and two inhalations from the pMDI (salmeterol/fluticasone or placebo Evohaler) upon rising and before going to bed; for symptom relief, as-needed inhalations were to be taken from the inhaler with the white grip (budesonide/formoterol or terbutaline Turbuhaler).

Efficacy measures

The primary objective of this study was to compare the efficacy of SMART [budesonide/formoterol (160/4.5 µg one inhalation bid) plus additional inhalations as needed], with salmeterol/fluticasone (25/125 µg two inhalations bid) plus terbutaline (0.4 mg/inhalation as needed). The primary variable was the time to first severe exacerbation. Severe exacerbations were defined as deterioration in asthma resulting in hospitalisation or emergency room (ER) treatment, or the need for oral steroids for ≥ 3 days (as judged by the investigator). To ensure that the results obtained were not specific to choice of ICS/LABA combination therapy or delivery device, predefined secondary objectives investigated were a combination of the efficacy of SMART vs. budesonide/formoterol (320/9 µg one inhalation bid) plus terbutaline (0.4 mg/inhalation as needed) both delivered by Turbuhaler, with an additional comparison of the efficacy between the two fixed-dose ICS/LABA regimen. Secondary outcome variables were the total numbers of severe exacerbations; inhalations of as-needed medication; change in morning and evening peak expiratory flow (PEF), FEV_1, asthma symptom score, nights with awakenings caused by asthma, symptom-free days, as-needed-free days, asthma-control days and the number of mild exacerbations.

Patients completed a daily diary throughout the study in which they recorded PEF, symptoms, reliever use and intake of maintenance medication. Adherence to prescribed treatment was checked by the investigator at every visit. Daytime and night-time asthma symptom scores, measured on a scale of 0–3 (where 0 = no symptoms and 3 = incapacitating symptoms), were also recorded; these scores were summed to obtain the total daily score (range 0–6). The percentage of symptom-free days, nights free of awakenings, reliever-free days and asthma control days (a night and a day without asthma symptoms, no night-time awakenings caused by asthma and no reliever use) were calculated from diary-card data. Mild exacerbation days, defined as a day with any one of the following: morning PEF ≥ 20% below baseline, daily as-needed medication use ≥ 2 inhalations above baseline or a night with an asthma-related awakening, were also calculated from diary-card data. A mild exacerbation was defined as two consecutive mild exacerbation days satisfying the same criterion.

FEV_1 was assessed by spirometry, performed as recommended by the European Respiratory Society (18), at each clinic visit. The best of three satisfactory FEV_1 tests was recorded (18,19). Following instruction, patients recorded morning and evening PEF using a Mini-Wright® peak flow meter (Clement Clarke, Harlow, UK). Measurements were to be carried out before inhalation of the study medication. The highest of three consecutive measurements was recorded.

The Asthma Control Questionnaire (ACQ) 5-item version (ACQ-5) (20,21) and Asthma Quality of Life Questionnaire [standardised version; AQLQ(S)] (22) were self-administered at clinic visits.

Tolerability was assessed by the recording of adverse events at clinic visits. Investigators were provided with a set of instructions to be used for the interpretation of causality judgement.

Overall ICS treatment load was compared between groups by converting ICS doses to beclomethasone dipropionate (BDP)-equivalent ICS doses. These calculations were based on the GINA (13) estimates of equipotence of ICS doses as metered doses: fluticasone 500 μg = budesonide 800 μg = beclomethasone 1000 μg; 800 μg budesonide metered dose = 640 μg delivered dose.

Statistical analysis

The study was powered to detect a difference in the primary end-point (time to first severe exacerbation). With a total of 1000 patients/group, a log-rank test (at the two-sided 5% significance level) had a 90% chance of detecting a difference between treatment groups, assuming a true difference of 20% vs. 14.5% in the proportion of patients experiencing a severe exacerbation (23). All patients with data after randomisation were included in the intention-to-treat population for all efficacy analyses. The safety analyses were based on all patients who received ≥ 1 dose of study drug.

The time to first severe exacerbation was described using Kaplan–Meier plots and was compared between treatments using a log-rank test. Further description of treatment differences was obtained using a Cox proportional hazards model stratified by country, with treatment as a factor. The total number of severe exacerbations was compared between treatment groups using a Poisson regression model, with treatment and country as factors and time in the study as an offset variable.

Changes in diary-card variables from the average value during run-in (average value over the last 10 days of run-in) to the average value during the treatment period were compared between treatments using an analysis of variance (ANOVA) model, with treatment and country as fixed factors and the run-in means as a covariate. Change in FEV_1 from baseline to the average value during visits 3–5 was analysed using a similar ANOVA, with baseline values as a covariate. The ACQ and AQLQ(S) overall scores were analysed in the same way as FEV_1, with the exception that, for AQLQ(S), the change from baseline to the last visit on treatment was used.

Results

Patient profile

Patient flow is summarised in Figure 1. Of the 4399 patients enrolled at 235 centres in 16 countries, 3335 were randomised to treatment. The most common reasons for exclusion from randomisation were failure to meet defined criteria for asthma severity, specifically spirometry criteria and use of as-needed medication during the run-in period. There were 409 protocol deviations in 327 patients, none of which justified exclusion of data from the analysis. Patient demographics are shown in Table 1. Self-reported adherence to maintenance medication was high; 99% of patients in all groups reported taking more than 81% of their maintenance medication.

Severe exacerbations

SMART prolonged the time to first severe exacerbation compared with fixed-dose salmeterol/fluticasone and budesonide/formoterol (log-rank test $p = 0.0034$ and $p = 0.023$ respectively; Figure 2). There was a 33% reduction in the hazard ratio (HR) for a first severe exacerbation with SMART compared with salmeterol/fluticasone [HR 0.67; 95% confidence interval (CI) 0.52–0.87; $p = 0.003$] and a 26% reduction compared with fixed-dose budesonide/formoterol (HR 0.74; 95% CI 0.56–0.96; $p = 0.026$). The two fixed-dose groups did not differ with respect to time to first severe exacerbation (Table 2). The total number of severe asthma exacerbations was reduced by 39% [relative rate (RR) 0.61; 95% CI 0.49–0.76; $p < 0.001$] in the SMART group compared with fixed-dose salmeterol/fluticasone and by 28% (RR 0.72; 95% CI 0.57–0.90; $p = 0.0048$) compared with fixed-dose budesonide/formoterol. The total number of exacerbations was similar in the two fixed-dose groups (Figure 3a).

The total number of hospitalisations/ER treatments was reduced in both budesonide/formoterol groups compared with the fixed-dose salmeterol/fluticasone group: there was a 39% rate reduction in the SMART group (RR 0.61; 95% CI 0.44–0.83; $p = 0.0015$) and a 32% reduction in the fixed-dose budesonide/formoterol group (RR 0.68; 95% CI 0.51–0.92; $p = 0.013$; Figure 3b). The difference between the two budesonide/formoterol groups was not statistically significant.

Table 1 Patients' baseline characteristics

Characteristic	Salmeterol/ fluticasone (n = 1123)	Budesonide/ formoterol (n = 1105)	SMART (n = 1107)
Male, *n* (%)	484 (43)	448 (41)	479 (43)
Mean age, years (SD)	38 (17)	38 (17)	38 (17)
Age, *n* (%)			
≥ 18 years	912 (81)	892 (81)	908 (82)
12–17 years	211 (19)	213 (19)	197 (18)
Smoking status			
Never, *n* (%)	904 (80)	865 (78)	873 (79)
Previous, *n* (%)	165 (15)	169 (15)	178 (16)
Current, *n* (%)	54 (5)	71 (7)	56 (5)
Mean FEV_1, % predicted (SD)	73 (14)	73 (14)	72 (14)
Mean FEV_1 reversibility, % (SD)	23 (12)	25 (14)	24 (12)
Mean ICS at study entry, μg/day (SD)	744 (230)	750 (262)	743 (240)
LABA use at study entry, *n* (%)	525 (47)	518 (47)	509 (46)

SMART, Symbicort® (budesonide/formoterol) maintenance and reliever therapy; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABA, long-acting β$_2$-agonist.

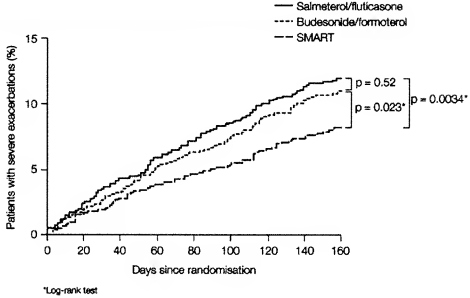

Figure 2 Time to first severe exacerbation (deterioration in asthma resulting in hospitalisation/emergency room treatment, or the need for oral steroids for ≥ 3 days). SMART, Symbicort® (budesonide/formoterol) maintenance and reliever therapy

The total exacerbation burden in days is shown in Table 2. The total number of days with exacerbations requiring oral steroid use was reduced by 41–45% with SMART compared with both fixed-dose regimens. Moreover, compared with fixed-dose treatment, SMART reduced the number of days with exacerbations requiring hospitalisation/ER treatment by 38–61% (Table 2).

A *post hoc* analysis, based on interaction between age-class and treatment, indicated that the size of the reduction in the overall exacerbation rate in the SMART group was consistent for adults (aged ≥ 18 years) and adolescents (aged < 18 years) (p = 0.84, interaction test). Adults treated with SMART had a 39% and 29% reduction in severe exacerbations vs. fixed-dose salmeterol/fluticasone ($p < 0.001$) and fixed-dose budesonide/formoterol ($p = 0.0043$) respectively. Similarly, the small number of adolescents treated with SMART had non-statistically significant reductions in severe exacerbations of 42% and 24% respectively.

Mild exacerbations

No significant differences were seen between the SMART group and the two fixed-dose regimens in the number of mild exacerbation days or the time to

Table 2 Exacerbation burden

Exacerbation burden	Salmeterol/ fluticasone	Budesonide/ formoterol	SMART	Treatment comparison of hazard ratios (95% CI) SMART vs. salmeterol/ fluticasone	SMART vs. budesonide/ formoterol	Budesonide/formoterol vs. salmeterol/ fluticasone
All event types						
No. patients having at least one severe exacerbation (%)*	138 (12)	126 (11)	94 (9)	0.67 (0.52, 0.87); p = 0.003	0.74 (0.56, 0.96); p = 0.026	0.91 (0.72, 1.16); p = 0.45
Rate/100 patients/6 months†	19	16	12	0.61 (0.49, 0.76); p < 0.001	0.72 (0.57, 0.90); p = 0.0048	0.85 (0.69, 1.04); p = 0.1
Total no. severe exacerbations (total no. days with event)	208 (1327)	173 (1143)	125 (692)			
Hospitalisation/ER treatment						
No. patients having at least one hospitalisation/ER treatment (%)*	70 (6)	50 (5)	48 (4)	0.69 (0.48, 0.99); p = 0.047	0.97 (0.65, 1.44); p = 0.87	0.71 (0.49, 1.02); p = 0.066
Rate/100 patients/6 months†	8	5	5	0.61 (0.44, 0.83); p = 0.0015	0.88 (0.63, 1.24); p = 0.47	0.68 (0.51, 0.92); p = 0.013
Total no. events (total no. days with event)	106 (378)	72 (124)	64 (108)			

*Cox proportional hazards model of time to first severe exacerbation; †Comparisons of relative rates from a Poisson regression. SMART, Symbicort® (budesonide/formoterol) maintenance and reliever therapy; ER, emergency room.

a mild exacerbation (two consecutive mild exacerbation days). There was an average of 27 mild exacerbation days/patient/6 months in the salmeterol/fluticasone group, 29 in the fixed-dose budesonide/formoterol group and 27 in the SMART group. Overall, 660 (59%), 689 (63%) and 674 (61%) salmeterol/fluticasone, budesonide/formoterol and SMART patients, respectively, experienced a mild exacerbation.

Asthma symptoms

SMART provided similar improvements to fixed-dose budesonide/formoterol and salmeterol/fluticasone in all symptom-control measures used to assess daily variability in asthma control (Table 3).

Asthma questionnaires

Patients in all three treatment groups reported similar improvements in AQLQ(S) and ACQ-5 scores. Changes of 0.5 units from run-in indicate clinically relevant improvements in both scores (21,24). These improvements were indicated by an increase in AQLQ(S) score of 0.76–0.78 (Figure 4a) and the reduction in ACQ-5 score of 0.74–0.79 in the three treatment groups (Figure 4b).

Lung function

FEV_1 and PEF values during the run-in and treatment periods are presented in Table 3. No differences between the three treatment groups in any of these measures were detected.

Overall treatment load

As-needed reliever medication use is shown in Table 3. As-needed use was similar in the SMART and fixed-dose groups, decreasing by 8–9 inhalations/week compared with baseline in all three groups. The range of daily mean BDP-equivalent ICS doses [calculations based on GINA estimations of equipotence of ICS in metered doses: fluticasone 500 μg = budesonide 800 μg = beclomethasone 1000 μg (13)] for the three treatment groups are summarised in Figure 5. While individual mean doses varied in SMART patients as a consequence of the treatment concept, there was an overall reduction in mean ICS dose in the SMART group compared with both fixed-dose groups. The overall number of days per treatment group when oral corticosteroids were required for asthma was 619 days in the SMART group, 1044 days with budesonide/formoterol and 1132 days with salmeterol/fluticasone.

Safety

All three treatments were well tolerated and there were no notable between-group differences in the number or severity of adverse events. The most frequently reported adverse events were upper respiratory tract infection, pharyngitis and nasopharyngitis. The incidence of pharmacologically predictable adverse events related to ICS and LABA use was low and comparable in all treatment groups.

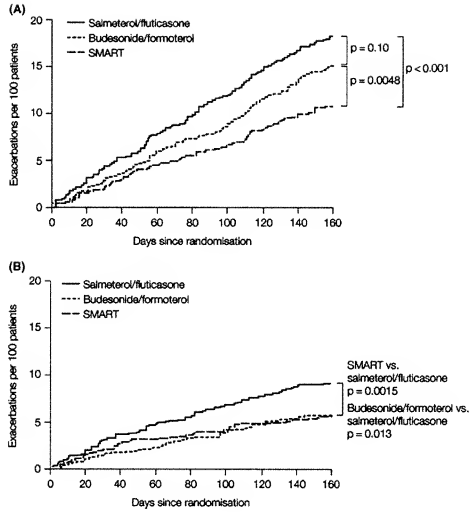

Figure 3 Cumulative rate of (A) severe exacerbations and (B) hospitalisations/ emergency room treatments caused by asthma; p-values are derived from relative rate analysis (Poisson regression analysis). SMART, Symbicort® (budesonide/ formoterol) maintenance and reliever therapy

Serious adverse events were uncommon and their incidence was comparable across all three treatment groups: 32 patients (3%) in the salmeterol/fluticasone group, 39 patients (4%) in the fixed-dose budesonide/ formoterol group and 31 patients (3%) in the SMART group experienced such events. Four serious adverse events were considered by the investigator to be causally related to the study drug: three in the SMART group (pneumonia, gastritis and asthma) and one in the salmeterol/fluticasone group (asthma).

Two deaths occurred during the study, one in the SMART group (respiratory failure) and one in the salmeterol/fluticasone group (cardiac failure). Neither death was considered by the investigator to be causally related to the study drug.

Discussion

This study validates the concept of SMART. Reducing the maintenance dose of budesonide/formoterol by 50% and using budesonide/formoterol as reliever medication instead of terbutaline reduces the risk and rate of severe exacerbations in adults and adolescents with asthma compared with a higher maintenance dose of fixed-dose budesonide/formoterol or salmeterol/fluticasone. Other measures of daily asthma control were similar across the three treatment groups. This improvement in the outcome of asthma treatment was seen even though the total dose of ICS administered using the SMART regimen was 25% lower in BDP equivalents than those administered in the fixed-dose regimens. Thus, while conventional fixed-dose combination therapy can provide well-controlled asthma for many patients, similar improvements can be achieved with the SMART approach while further reducing exacerbations and drug load.

The reduction in exacerbations and associated medical care was substantial. Patients in the SMART group had 28–39% fewer exacerbations than those in the fixed-dose groups. Extrapolating these 6-month data to a 1-year period suggests

Table 3 Clinical outcomes

Efficacy end-point	Salmeterol/ fluticasone	Budesonide/ formoterol	SMART	Treatment comparison of clinical outcomes; mean difference (95% CI)		
				SMART vs. salmeterol/ fluticasone	SMART vs. budesonide/ formoterol	Budesonide/formoterol vs. salmeterol/fluticasone
Asthma symptoms						
Total score (0–6)						
Run-in	1.94	1.93	1.91	0.04 (−0.03, 0.10)	0.00 (−0.07, 0.06)	0.04 (−0.02, 0.11)
Treatment	1.03	1.07	1.06			
Symptom-free days (%)						
Run-in	8.6	8.8	9.3	−2.5 (−5.3, 0.3)	−0.8 (−3.6, 2.0)	−1.6 (−4.4, 1.2)
Treatment	46.0	44.6	44.2			
Asthma-control days* (%)						
Run-in	5.7	5.9	5.8	−2.6 (−5.4, 0.2)	−0.7 (−3.6, 2.1)	−1.9 (−4.7, 1.0)
Treatment	43.7	42.2	41.3			
Night-time awakenings (%)						
Run-in	31.5	32.8	33.7	−0.8 (−2.4, 0.9)	−1.8 (−2.6, 0.7)	0.2 (−1.4, 1.8)
Treatment	14.0	14.6	14.1			
Use of as-needed medication						
Total no. inhalations/day						
Run-in	2.33	2.31	2.29	0.07 (−0.02, 0.16)	−0.03 (−0.12, 0.06)	0.10 (0.01, 0.19)†
Treatment	0.96	1.05	1.02			
As-needed-free days (%)						
Run-in	8.8	8.8	8.9	−3.2 (−6.0, −0.5)†	−1.8 (−4.6, 1.0)	−1.4 (−4.2, 1.4)
Treatment	59.1	57.8	56.0			
Lung function						
FEV_1 (l)						
Visit 2	2.43	2.42	2.44	0.006 (−0.025, 0.037)	0.005 (−0.026, 0.037)	0.000 (−0.031, 0.031)
Visit 3–5 (mean)	2.67	2.66	2.69			
Morning PEF (l/min)						
Run-in	338	335	337	−3.2 (−6.9, 0.4)	−0.7 (−4.5, 3.0)	−2.5 (−6.2, 1.2)
Treatment	367	362	363			
Evening PEF (l/min)						
Run-in	342	344	346	−1.3 (−4.9, 2.3)	−0.6 (−4.3, 3.0)	−0.7 (−4.3, 3.0)
Treatment	376	366	368			

*Asthma-control days were defined as a day with no symptoms (day or night), no awakenings caused by asthma and no as-needed medication use; †Statistically different at the 5% level of significance. SMART, Symbicort® (budesonide/formoterol) maintenance and reliever therapy; FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; CI, confidence interval.

that treating 100 matched patients for 1 year with SMART compared with fixed-dose salmeterol/fluticasone and fixed-dose budesonide/formoterol would prevent 15 and 9 severe exacerbations respectively (the number needed to treat to prevent one exacerbation was 7 and 11 respectively). There were fewer exacerbations requiring hospitalisation or ER treatment in the SMART group, with such events occurring on 61% fewer days compared with salmeterol/fluticasone and on 38% fewer days compared with fixed double-dose budesonide/formoterol. Exacerbations leading to ER treatment or hospitalisation were approximately 1 day longer on average (based on the number of days with these events) in the fixed-dose salmeterol/fluticasone vs. the SMART group.

It seems unlikely that the reduced number of SMART patients who still experienced exacerbations did so as a result of using a maintenance dose that was too low. All patients using fixed-combination ICS/LABA in our study received the equivalent of the maximally effective dose used in the landmark FACET exacerbation study (25). With SMART, the average dose used approached 75% of the FACET dose. Nevertheless, SMART resulted in further reductions in exacerbations of all types vs. both fixed-dose groups. This suggests that the SMART approach has exceeded a previous gold standard for exacerbation control, while reducing overall steroid and LABA doses.

The precise reason for the overall reduction in exacerbations with the SMART approach remains to

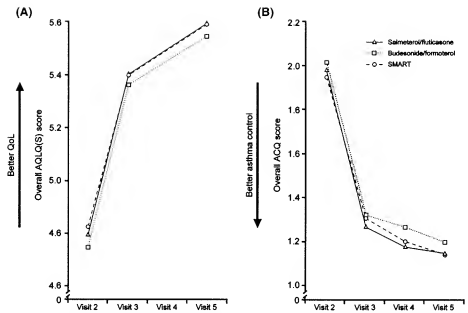

Figure 4 Mean overall (A) Asthma Quality of Life Questionnaire (standardised version) [AQLQ(S)] and (B) Asthma Control Questionnaire (ACQ) scores over the duration of the study. QoL, quality of life; SMART, Symbicort® (budesonide/formoterol) maintenance and reliever therapy

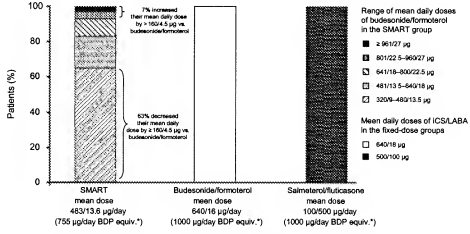

Figure 5 Range of daily mean doses of ICS/LABA reported by individual study patients. *Mean ICS doses converted to BDP equivalents based on GINA (13) guidelines. Compared with fixed-dose budesonide/formoterol treatment, 9 : 1 (ratio: 63% divided by 7%) SMART-treated patients reduced their mean daily dose by at least 160/4.5 µg than increased their dose by at least 160/4.5 µg. SMART, Symbicort® (budesonide/formoterol) maintenance and reliever therapy; BDP, beclomethasone dipropionate

be fully elucidated. Temporary dose increases resulting from as-needed formoterol and budesonide are likely to contribute to the overall efficacy of this treatment. As-needed treatment immediately following exposure to environmental triggers that lead to a temporary loss of symptom control is likely to result in an increase in controller therapy in line with disease activity. During periods when asthma control is stable, with no need for symptom relief (56% of study days), patients using the SMART approach default solely to maintenance budesonide/formoterol, but at half the daily dose compared with the fixed-dose regimen. Thus, maintenance plus as-needed budesonide/formoterol responds more effectively and efficiently to the natural variations in asthma control that are evident even when using an ICS/LABA regimen at a higher daily dose.

Timely increases in the ICS dose have been suggested as the defining feature of SMART (9,26,27). Thus, budesonide-containing reliever therapy can ensure that an increase in anti-inflammatory therapy is delivered as required during periods of deteriorating symptoms and increased need for reliever medication (28). In our study, SMART patients used more budesonide/formoterol than the fixed-dose budesonide/formoterol group on only 13% of days, with half the dose used on 56% of days. This suggests that the timing of the dose increase, not the overall dose, is of greater importance. Whether this benefit is related to dose clustering of the as-needed ICS over a spread of days, or to the more efficient spread of the dose throughout the day during periods of poor control, is not clear.

Studies have shown that increasing the dose and frequency of administration of ICS improves asthma control in patients with acute worsenings (29). As lung tissue concentrations of ICS decline between maintenance doses (30,31), as-needed ICS may restore concentrations when the level of ICS can be suboptimal. In contrast, approaches that rely on a significant deterioration in asthma symptoms and action plans that instruct patients to double their ICS dose without an increase in dose frequency have been demonstrated to be wholly ineffective at preventing exacerbations (32,33).

Marked improvements in daily symptom control were seen in all three treatment groups, despite patients in the SMART group using a lower maintenance dose of ICS/LABA. Compared with run-in, patients in all groups experienced similar improvements in asthma control and quality of life (assessed by questionnaires) and more asthma-control days and fewer asthma-related awakenings (assessed by daily diaries). The increase in day-to-day asthma control seen in all three groups can be extrapolated to at least 130 extra days per year with full symptom control without the use of reliever medication and at least 64 extra nights per year without awakenings. There was no evidence of any clinically relevant between-group differences in any of these control measures. Numbers of days with symptom flares (mild exacerbation days) were equally distributed among the three treatment groups. Furthermore, no differences in lung function were detected between the treatment groups, despite lower use of bronchodilator therapy (maintenance and as needed) in the SMART group. The mean daily ICS dose in BDP equivalents (13) was approximately 750 μg in the SMART group vs. 1000 μg in both fixed-dose groups. In total, only eight SMART patients (< 1%) used a mean dose of budesonide equivalent to > 2000 μg/day of BDP. The majority of SMART patients used less ICS and less LABA than in the fixed-dose budesonide/formoterol group, i.e. for every SMART patient who took 160/4.5 μg/day of budesonide/formoterol more than in the fixed-dose group, there were nine SMART patients using at least 160/4.5 μg/day less. The fact that day-to-day symptom control was similar in all three groups, even with the clear difference observed in severe exacerbation rates, serves as a reminder that these measures reflect different aspects of asthma control, both of which need to be considered when evaluating asthma management programmes. Our results show the improved control seen with as-needed budesonide/formoterol using the SMART concept vs. fixed-dose ICS/LABA + SABA therapy is greater for exacerbations than for minor symptoms. Minor symptoms dictate the need for an increase in as-needed therapy to a similar extent in all treatment groups, but with the SMART asthma management approach this leads to an increase in anti-inflammatory therapy at the right time, resulting in fewer exacerbations.

Although there were no clinically important differences between the two fixed-dose groups in the majority of outcomes, one clinically relevant and statistically significant advantage of budesonide/formoterol was observed. Patients treated with fixed-dose budesonide/formoterol had 32% fewer exacerbations requiring hospitalisation/ER treatment vs. those in the salmeterol/fluticasone group. It is noteworthy that this is the largest study ever performed with two fixed-dose ICS/LABA combinations and, as such, may be the first study able to detect such differences. A similar trend was seen in a smaller study (approximately 200 patients in each group) in which three vs. eight events required hospitalisation/ER treatment in patients treated with the same fixed dose of budesonide/formoterol or salmeterol/fluticasone respectively (1). The reasons for this difference remain unclear and may require further exploratory analysis. One possible reason may be that formoterol, a full β_2-agonist, is more efficacious than salmeterol, a partial β_2-agonist, during periods of increased inflammation or challenge (34,35). Another factor may be the beneficial effects on neutrophilic inflammation that have been described for formoterol but to a lesser extent for salmeterol (36).

In a controlled clinical setting, SMART has previously been shown to improve asthma control compared with the same maintenance dose of budesonide/formoterol plus terbutaline for relief (9). In a study allowing titration of the maintenance dose as judged appropriate by the treating physician, SMART patients had fewer exacerbations and better asthma control than those receiving salmeterol/fluticasone up to a dose of 50/500 μg bid (40% of

patients) (12). Together these studies suggest that SMART is uniquely effective at reducing exacerbations and their associated morbidity compared with fixed-dose ICS/LABA, even at a higher daily dose. The study by Vogelmeier et al. was performed open label to allow easier maintenance-dose titration; we have now demonstrated in a very large double-blind study that SMART leads to fewer exacerbations with no increase in fluctuations of daily asthma control compared with a twofold higher maintenance dose of budesonide/formoterol or a corresponding dose of salmeterol/fluticasone. The SMART approach has also been demonstrated to deliver significant cost savings compared with the higher maintenance dose of budesonide/formoterol or salmeterol/fluticasone plus terbutaline as needed, when applying 2004 UK unit costs to the present dataset (37).

In the present study, patients who were infrequent users of reliever medication were excluded after the run-in period. This may have excluded a small minority of patients for whom the benefit of SMART is unknown. Nonetheless, a recent survey of 1921 patients using regular ICS or ICS/LABA medication has highlighted that 71% of these patients used their reliever medication every day and 47% had experienced one or more exacerbations in the previous year (7), suggesting that the results of the present study have wide-reaching applicability to real-life asthma. Finally, this study, in addition to previous research (9–11), has confirmed that the SMART treatment approach is well tolerated with no increase in asthma-related events of any type compared with higher doses of ICS alone or an alternative combination ICS/LABA regimen.

In conclusion, compared with a twofold higher fixed maintenance dose of budesonide/formoterol or a corresponding dose of salmeterol/fluticasone plus SABA for relief, SMART reduces the incidence of severe asthma exacerbations and maintains similar daily asthma control at a lower overall drug load. With this combination of increased efficacy and simplicity, the SMART approach represents a significant improvement over fixed, twice-daily combinations of higher-dose ICS/LABA, which have until now been regarded as the most effective way to manage moderate and severe persistent asthma.

Acknowledgements

We thank the study investigators for their outstanding work in conducting the trial. We thank Anette Bjärdahlen (AstraZeneca, Lund, Sweden), the study team leader; Stefan Peterson (AstraZeneca, Lund, Sweden), who performed all data analyses; Tomas LG Andersson (AstraZeneca, Lund, Sweden), who contributed to the interpretation of the results and the compilation of the manuscript; Allan Harris (AstraZeneca, Lund, Sweden), who was responsible for the development of the study concept and Deirdre Carman (Adelphi Communications Ltd) who provided medical writing support on behalf of AstraZeneca. This study was funded by AstraZeneca, Lund, Sweden.

Supplementary material

The following supplementary material is available for this article online:

Slideshow S1. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations.

This material is available as part of the online article from http://www.blackwell-synergy.com

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Paper received January 2007, accepted February 2007

Articles

Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study

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Lancet 2006; 368: 744–53

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Summary

Background The contributions of as-needed inhaled corticosteroids and long-acting β2-agonists (LABA) to asthma control have not been fully established. We compared the efficacy and safety of three reliever strategies: a traditional short-acting β2 agonist; a rapid-onset LABA (formoterol); and a combination of LABA and an inhaled corticosteroid (budesonide-formoterol) in symptomatic patients receiving budesonide-formoterol maintenance therapy.

Methods We did a 12-month, double-blind, parallel-group study in 3394 patients (aged 12 years or older), in 289 centres in 20 countries, who were using inhaled corticosteroids at study entry and symptomatic on budesonide-formoterol (160 μg and 4·5 μg, respectively), one inhalation twice daily, during a 2-week run-in. After run-in, patients were randomly assigned budesonide-formoterol maintenance therapy plus one of three alternative as-needed medications—terbutaline (0·4 mg), formoterol (4·5 μg), or budesonide-formoterol (160 μg and 4·5 μg). The primary outcome was time to first severe exacerbation, defined as an event resulting in hospitalisation, emergency room treatment, or both, or the need for oral steroids for 3 days or more.

Findings Time to first severe exacerbation was longer with as-needed budesonide-formoterol versus formoterol ($p=0·0048$; log-rank test) and with as-needed formoterol versus terbutaline ($p=0·0051$). The rate of severe exacerbations was 37, 29, and 19 per 100 patients per year with as-needed terbutaline, formoterol, and budesonide-formoterol, respectively (rate ratios budesonide-formoterol versus formoterol 0·67 [95% CI 0·56–0·80; $p<0·0001$]; budesonide-formoterol versus terbutaline 0·52 [0·44–0·62; $p<0·0001$]; formoterol versus terbutaline 0·78 [0·67–0·91; $p=0·0012$]). Asthma control days increased to a similar extent in all treatment groups. As-needed formoterol did not significantly improve symptoms compared with as-needed terbutaline. All treatments were well tolerated.

Interpretation Both monocomponents of budesonide-formoterol given as needed contribute to enhanced protection from severe exacerbations in patients receiving combination therapy for maintenance.

Introduction

Over the past decade, maintenance treatment in patients with persistent asthma has evolved from inhaled corticosteroids alone to combination therapy with long-acting β2 agonists (LABA). This move has led to improved symptom control and a reduced need for higher doses of inhaled corticosteroids.[1–3] However, despite evidence that add-on LABA therapy can reduce exacerbations by 3–14% compared with higher doses of inhaled corticosteroids,[4] the dose of inhaled steroid at which the addition of LABA is most beneficial has not been clearly established.[3]

This dilemma could be overcome if a pragmatic way of delivering increased anti-inflammatory therapy at the first sign of increased symptoms were found, rather than relying on as-needed short-acting β2 agonists. In clinical studies, the use of a combination of inhaled corticosteroids and LABA (budesonide-formoterol) in one inhaler for both maintenance and as-needed therapy reduced the risk of experiencing severe exacerbations by 39–54% compared with a higher maintenance dose of budesonide,[5–8] by 45% compared with fixed-dose budesonide-formoterol,[9] and by 25% compared with a higher dose of salmeterol-fluticasone.[10] Moreover, this novel treatment approach reduced both inhaled corticosteroids and oral corticosteroid exposure, with a similar or reduced effect on morning plasma cortisol and adrenal function, compared with budesonide 800 μg per day.[5,10]

This simplified approach is possible because formoterol provides rapid symptom relief,[11–14] with the result that a separate short-acting β2 agonist is not needed. However, the mechanism underlying the reduction in exacerbations seen with budesonide-formoterol maintenance and reliever therapy is not fully understood. As-needed formoterol was shown to reduce asthma exacerbations compared with terbutaline in a large, double-blind study in asthma patients with a persistent high use of reliever therapy despite using regular inhaled corticosteroids.[15] However, whether patients on combination therapy would experience such a benefit was not clear. Additionally, the specific contribution of the as-needed budesonide component of budesonide-formoterol for maintenance and relief has not been assessed. The present 12-month, double-blind study was therefore done in patients with moderate to severe persistent asthma who remained symptomatic on regular budesonide-formoterol

combination maintenance therapy, to assess the add-on efficacy of three alternative reliever medications—budesonide-formoterol, formoterol, and terbutaline.

Methods

Patients

Outpatients aged 12 years or older with a clinical diagnosis of asthma[11] for at least 6 months were enrolled if they had had more than one severe asthma exacerbation in the 12 months before entry. All patients had used inhaled corticosteroids for at least 3 months and at a constant dose for 4 weeks or more immediately before entry. Inclusion criteria also included a forced expiratory volume in 1 s (FEV_1) 50–100% of predicted normal (prebronchodilator) with 12% reversibility or more (and an increase in basal FEV, of 200 mL or more if aged 18 years or older) after inhalation of terbutaline 1 mg. Exclusion criteria included any respiratory infection affecting the patient's asthma or use of oral corticosteroids within 1 month of study entry. To be eligible for randomisation, patients had to have used reliever medication on 5 or more of the last 7 days of run-in, but no more than ten inhalations on any one day.

Study design

Our 12-month, double-blind, randomised parallel-group study was done in 289 centres in 20 countries: Belgium (21 centres), Bulgaria (11), China (6), Czech Republic (34), Germany (26), Greece (9), Hungary (20), Indonesia (6), Italy (6), Malaysia (3), The Netherlands (30), Norway (17), the Philippines (11), Poland (18), Romania (12), Russia (11), Slovakia (12), South Africa (30), South Korea (4), and Vietnam (2). The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Independent ethics committees approved the study protocol, patient information, and consent forms. All patients and parents or guardians of underage children gave written informed consent.

Patients attended clinic visits at the beginning and end of run-in, and after 1, 4, 8, and 12 months of treatment (visits 1–6). During a 2-week run-in period, patients used budesonide-formoterol 160/4·5 μg (symbicort turbuhaler, AstraZeneca, Lund, Sweden), one inhalation twice a day, plus terbutaline 0·5 mg (metered dose; delivered dose 0·4 mg; bricanyl turbuhaler, AstraZeneca) for reliever medication. After run-in, all patients continued to use budesonide-formoterol 160/4·5 μg, one inhalation twice a day for maintenance therapy and were randomly assigned to treatment with one of three reliever medications (1:1:1 ratio) for 12 months: additional inhalations of budesonide-formoterol 160/4·5 μg; formoterol 4·5 μg (oxis turbuhaler, AstraZeneca); or terbutaline 0·4 mg. All as-needed study medication was given via identical turbuhaler inhalers, all matched in appearance to the symbicort turbuhaler.

The randomisation schedule was computer generated at AstraZeneca Research and Development, Charnwood, UK, by a person independent of the study team. Within each centre, eligible patients were sequentially assigned a randomisation code by the investigator from the computer-generated list.

Patients were instructed to use their reliever medication for asthma symptoms but not for prophylaxis. During the treatment, patients were not to use more than ten inhalations of reliever medication a day. If more than ten inhalations were needed in one day, patients were told to contact the investigator for reassessment.

Procedures

The primary outcome measure was time to first severe exacerbation. The total number of severe exacerbations, number of days with hospitalisation, emergency room treatment, or both, and days with oral steroids because of exacerbations were recorded. Secondary outcomes included total number of severe exacerbations, time to first and total number of emergency treatment or hospitalisations, asthma symptom scores—asthma control questionnaire (five-item symptom and activity version; ACQ-5) score;[9] mild exacerbations; FEV_1; morning and evening peak expiratory flow (PEF); and reliever medication use. Patients completed a daily diary throughout the study in which they recorded asthma symptoms during the night and daytime (on a three point scale, with 0 indicating no symptoms and three indicating incapacitating symptoms). These scores were added to obtain the total daily asthma symptom score (range 0–6). Nights with awakenings due to asthma, the number of inhalations of reliever medication, and intake of maintenance medication were also recorded on diary cards. The percentage of asthma-control days (a night and a day with no asthma symptoms, no intake of reliever medication, and a night with no awakenings due to asthma symptoms) were assessed. The ACQ-5 was completed by patients at every clinic visit, with all five questions scored on a scale of 0 to 6 (where 0 represents good control and 6 represents poor control).[9]

At each clinic visit, the best of three satisfactory FEV, tests was recorded. Patients recorded the best of three PEF measurements with a Mini-Wright peak flow meter (Clement Clarke, Harlow, UK) on rising in the morning and before going to bed. Adverse events reported spontaneously and in response to a standard question at visits 2–6 were recorded.

A severe exacerbation was defined as deterioration in asthma resulting in emergency treatment or hospitalisation or the need for oral steroids for 3 days or more (as judged by the investigator). A mild exacerbation day was defined as fulfilment of at least one of the following criteria, based on 24 h diary data: any night with awakenings due to asthma; morning PEF 20% or more below baseline (average of previous 10 days before the day of randomisation) of morning PEF; as-needed medication use of two inhalations or more in 24 h above baseline (the average of previous 10 days before the day of randomisation).

A mild exacerbation was defined as two consecutive mild asthma exacerbation days satisfying the same criterion.

Statistical analysis

The primary objective was to compare budesonide-formoterol maintenance and as needed versus budesonide-formoterol with formoterol as needed. A secondary objective was to compare budesonide-formoterol for maintenance and as needed with budesonide-formoterol with terbutaline as needed. The primary outcome variable was time from randomisation to the first severe asthma exacerbation. With a total of 1000 patients per group, a log-rank test (at the two-sided 5% significance level) had a 90% chance of detecting a difference, assuming a true difference of 25% versus 19% in the proportion of patients with severe exacerbation. All patients for whom data were recorded after randomisation were included in the full analysis set, which was used for all efficacy analyses. The safety analyses were based on all patients who received one dose or more of the randomised study drug and who had data recorded after randomisation.

The time to first severe exacerbation was described with Kaplan–Meier curves and was compared between treatments with a log-rank test. Further description of treatment differences was obtained with a Cox proportional hazards model stratified by country and with treatment as factor.

Several secondary outcome variables were used to further compare the efficacy of the three treatments. The total number of severe exacerbations was compared between treatment groups using a Poisson regression model, with treatment and country as factors and time in the study as an offset variable. Time to first mild exacerbation and the total number of mild exacerbation days were analysed in the same way as severe exacerbations.

Changes in diary-card variables from the average value during run-in (average value over the previous 10 days of run-in) to the average value during treatment were

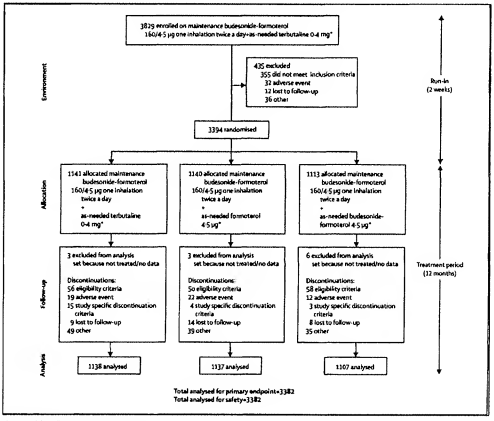

Figure 1: Trial profile
*0·4 mg delivered dose corresponds to 0·5 mg metered dose.

	Terbutaline as-needed group (n=1141)	Formoterol as-needed group (n=1140)	Budesonide–formoterol as-needed group (n=1113)
Men, n (%)	450 (39%)	458 (40%)	437 (39%)
Age, years	43 (12–83)	42 (12–81)	42 (12–89)
Median (range) asthma duration, years	10 (1–69)	10 (1–77)	9 (0–64)
FEV$_1$, l	2·16 (0·68–4·58)	2·20 (0·74–4·58)	2·23 (0·61–4·68)
FEV$_1$ (pre-terbutaline), % predicted	72 (391–100)	72 (381–1151)	72 (301–1101)
FEV$_1$ reversibility, %	24 (111–90)	24 (01–96)	24 (61–132)
ICS dose at entry, µg/day	753 (250†–1600)	758 (320†–1600)	757 (1501–1600)†
Inhaled LABA use at entry, % of patients	59%	59%	59%
Mean daily asthma control measures ‡			
Total asthma symptom score (scale 0–6)	1·74 (0·00–6·00)	1·70 (0·00–6·00)	1·73 (0·00–5·71)
Reliever use, number of inhalations per 24 h	1·9 (0·3–9·7)	1·9 (0·0–9·3)	1·8 (0·0–8·9)
Nights with awakenings, %	30·3 (0–100)	28·0 (0–100)	33·1 (0–100)
Asthma-control days§, %	8·3 (0–50)	8·3 (0–80)	9·2 (0–90)
ACQ-5¶	1·9 (0–4·8)	1·9 (0·4–4·8)	1·9 (0·4–4·8)

Data are mean (range) unless otherwise indicated. ACQ-5=Asthma control questionnaire (5-item symptom and activity version). FEV$_1$=forced expiratory volume in 1 s. ICS=inhaled corticosteroid. LABA=long-acting β2 agonist. *All patients received budesonide–formoterol 160/4·5 µg one inhalation twice daily for maintenance therapy. †Deviation from inclusion criteria (included in all statistical analyses). ‡Average over the past 10 days of run-in. §0·5 night and day with no asthma symptoms (symptom score=0), a night with no awakenings due to asthma symptoms, and a night and day with no use of as-needed medication. ¶ACQ-5 was measured at visit 2.

*Table 1: Baseline characteristics of patients using maintenance budesonide–formoterol plus alternative reliever medications**

compared between treatments with an ANOVA model with treatment and country as fixed factors and the run-in period average as a covariate. Changes in FEV$_1$ and ACQ-5 were analysed with a similar ANOVA, with the end of run-in value as a covariate. Results for secondary outcome variables are reported with nominal p values, without any adjustment for multiple tests. Adverse events were analysed with descriptive statistics and qualitative analysis.

Role of the funding source

The sponsors of the study were involved with the study design, interpretation of the data, and the decision to submit the paper for publication in conjunction with the study investigators. Employees of the sponsor collected and managed the data, and performed the data analysis. The corresponding author had access to the full clinical trial database and all authors had free access to the clinical study report and the results of the statistical analyses. Employees of the sponsor reviewed drafts of the manuscript and made editing suggestions. All authors made final decisions on all aspects of the manuscript.

Results

The first patient was enrolled into the study on April 10, 2003, and the last patient completed the study on Dec 21, 2004. Of the 3829 patients enrolled in the study, 3394 were randomised. Of the 435 patients (11%) who were not randomised, 355 did not satisfy eligibility criteria, 32 had an adverse event, 12 were lost to follow-up, and 36 discontinued for other reasons. The full analysis set included all randomised patients who provided any data after randomisation. Data were not obtained for 12 randomised patients before they left the study. Therefore, 3382 patients were included in the efficacy and safety analyses (figure 1). There were 474 patients with one protocol deviation or more, with a similar distribution across groups. The mean number of protocol deviations per patient was 0·2 (range 1–10); none of the deviations justified exclusion of data from the analysis. Baseline characteristics were comparable

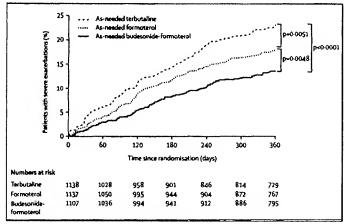

Figure 2: Kaplan–Meier plot of time to first severe asthma exacerbation
Time to first severe asthma exacerbation defined as a deterioration in asthma resulting in hospitalisation, emergency room treatment, or the need for oral steroids for 3 days or more because of asthma (as judged by investigator). Patients received maintenance budesonide–formoterol 160/4·5 µg, one inhalation twice daily, plus one of the following for as-needed relief: additional inhalations of budesonide–formoterol 160/4·5 µg, formoterol 4·5 µg, or terbutaline 0·4 mg. Significant between-group differences were derived from a log-rank test.

	Reliever medication group			Treatment comparison of hazard ratios (95% CI)		
	Terbutaline as-needed (n=1338)	Formoterol as-needed (n=1337)	Budesonide-formoterol as-needed (n=1107)	Formoterol versus terbutaline	Budesonide-formoterol versus terbutaline	Budesonide-formoterol versus formoterol
Severe exacerbations (all definitions)						
Patients with event, n (%)	245 (22%)	195 (17%)	143 (13%)	0·76* (0·63–0·92); p=0·004	0·55* (0·45–0·68); p<0·0001	0·73* (0·59–0·90); p=0·0038
Total events (days with events)	377 (3030)	296 (2214)	194 (1353)			
Rate, events per 100 patients per year	37	29	19	0·78† (0·67–0·91); p=0·0012	0·52† (0·44–0·62); p<0·0001	0·67† (0·56–0·80); p<0·0001
Emergency room visits or hospitalisations						
Patients with event, n (%)	91 (8%)	75 (7%)	54 (5%)	0·79* (0·58–1·07); p=0·12	0·57* (0·41–0·81); p=0·0013	0·73* (0·53–1·04); p=0·079
Total events (days with events)	115 (392)	98 (282)	70 (218)			
Rate, events per 100 patients per year	7	5	4	0·83† (0·63–1·08); p=0·17	0·61† (0·45–0·82); p=0·0010	0·73† (0·54–0·99); p=0·046
Mild exacerbations						
Patients with event, n (%)	887 (78%)	873 (77%)	811 (74%)	0·97* (0·88–1·06); p=0·47	0·88* (0·80–0·97); p=0·0075	0·91* (0·83–1·00); p=0·050
Rate, days per patient per year	69	63	57	0·91† (0·83–1·00); p=0·058	0·82† (0·74–0·91); p=0·0001	0·90† (0·81–1·00); p=0·043

All patients received budesonide-formoterol 160/4·5 μg one inhalation twice daily for maintenance therapy. *Treatment comparisons of hazard ratios from a Cox proportional hazards model of time to first severe exacerbation. †Comparisons of relative rates from a Poisson regression.

Table 2: Severe and mild asthma exacerbations in patients using maintenance budesonide-formoterol plus alternative reliever medications

See Online for webtable

between groups (table 1). Self-reported adherence to maintenance medication was equally high in all groups (99% of patients had an average use of at least 1·7) maintenance inhalations per day).

The time to first severe exacerbation was prolonged with budesonide-formoterol for maintenance and relief versus budesonide-formoterol plus formoterol (p=0·0048, log-rank test) or terbutaline (p<0·0001; figure 2). As-needed formoterol prolonged the time to first severe exacerbation versus terbutaline (p=0·0051). As-needed budesonide-formoterol reduced the instantaneous risk of a severe exacerbation by 27% (95% CI 10–41%) versus formoterol and by 45% (32–55%) versus terbutaline. The risk reduction with as-needed formoterol versus terbutaline was 24% (8–37%). There were 867 severe exacerbations during the study (table 2). The yearly rate per patient was reduced with as-needed budesonide-formoterol by 33% versus formoterol (20–44%; p<0·0001), by 48% versus terbutaline (38–56%; p<0·0001), and by 22% with as-needed formoterol versus terbutaline (9–33%; p=0·0012; table 2). Rates of exacerbations needing emergency room treatment or hospitalisation—the most robust definition of exacerbations—were also reduced with as-needed budesonide-formoterol by 27% (3–46%; p=0·046) versus formoterol and by 39% (18–55%; p=0·0010) versus terbutaline, respectively. There was no significant difference between formoterol and terbutaline in this outcome (table 2). The proportion of patients with more than one exacerbation was low in all three treatment groups and lowest in the as-needed budesonide-formoterol group (3%, 7%, and 7% of patients in the as-needed budesonide-formoterol, formoterol, and terbutaline groups, respectively; webtable). Mild exacerbation days, a composite measure of poor control days, were reduced by 10–18% with as-needed budesonide-formoterol compared with both formoterol (p=0·043) and terbutaline (p<0·0001). The time to first mild exacerbation (defined as two consecutive mild exacerbation days satisfying the same criterion) was also longer with as-needed budesonide-formoterol versus terbutaline (p=0·0080) but the difference between as-needed budesonide-formoterol and formoterol was not significant (p=0·059). Mean asthma symptom scores decreased from run-in for all groups, with a greater reduction in the budesonide-formoterol for maintenance and reliever therapy group versus maintenance therapy plus formoterol (p=0·0002) or terbutaline (p=0·0007; table 3). Night-time awakenings were reduced by 2% (7 nights per year) with as-needed budesonide-formoterol versus formoterol (p=0·018) and by 3% versus terbutaline (p=0·0025). Improvements were maintained during the 12-month study (webfigure). No between-group differences were seen with as-needed formoterol compared with terbutaline for asthma symptom scores or night-time awakenings (table 3). Asthma-control days (days without symptoms or reliever use) increased in all groups from run-in, with no between-group differences (table 2). Overall ACQ-5 scores improved to a greater extent with as-needed budesonide-formoterol than with formoterol (p=0·0009) and terbutaline (p<0·0001). No difference in overall ACQ-5 scores was seen with formoterol versus terbutaline (table 3).

See Online for webfigure

Mean FEV$_1$ improved in each of the treatment groups during run-in when all patients used maintenance budesonide-formoterol plus as-needed terbutaline. After

	Change from run-in			Treatment comparison (95% CI); p*		
	Terbutaline as-needed (n=1138)	Formoterol as-needed (n=1137)	Budesonide-formoterol as-needed (n=1107)	Formoterol versus terbutaline	Budesonide-formoterol versus terbutaline	Budesonide-formoterol versus formoterol
Symptom control						
Asthma symptom score (scale 0–6)†	-0·58	-0·57	-0·69	0·01 (-0·05 to 0·07); p=0·72	-0·11 (-0·17 to -0·05); p=0·0007	-0·12 (-0·18 to -0·06); p=0·0002
Reliever use, number of inhalations per 24 h†	-0·64	-0·67	-0·84	-0·03 (-0·11 to 0·05); p=0·48	-0·20 (-0·28 to -0·11); p<0·0001	-0·17 (-0·25 to -0·08); p<0·0001
Nights with awakenings, %‡	-13·5%	-14·0%	-16·0%	-0·6 (-2·2 to 1·1); p=0·51	-2·6 (-4·3 to -0·9); p=0·0025	-2·0 (-3·7 to -0·4); p=0·0118
Asthma-control days, %‡	29·3%	28·8%	31·2%	-0·5 (-3·1 to 2·2); p=0·74	1·9 (-0·7 to 4·6); p=0·15	2·4 (-0·3 to 5·1); p=0·079
ACQ-5§	-0·49	-0·53	-0·63	-0·04 (-0·10, 0·02); p=0·21	-0·15 (-0·21, -0·08); p<0·0001	-0·11 (-0·17, -0·04); p=0·0009
Lung function¶						
FEV$_1$ (L)‖	-0·02	0·01	0·06	0·03 (0·001 to 0·05); p=0·043	0·08 (0·05 to 0·10); p<0·0001	0·05 (0·02 to 0·08); p=0·00014
Morning PEF (L/min)†	7·9	10·6	15·3	2·7 (-0·6 to 5·9); p=0·11	7·5 (4·2 to 10·7); p<0·0001	4·8 (1·5 to 8·0); p=0·0040
Evening PEF (L/min)†	7·5	8·5	13·8	0·9 (-2·3 to 4·1); p=0·57	6·3 (3·1 to 9·5); p=0·00014	5·4 (2·1 to 8·6); p=0·0011

All patients received budesonide-formoterol 160/4·5 µg one inhalation twice daily for maintenance therapy. ACQ=Asthma Control Questionnaire (5-item symptom and activity version); PEF=peak expiratory volume in 1 s; PEF=peak expiratory flow; †ANOVA; ‡Data are presented as adjusted mean change from run-in in the treatment period. §Data are presented as adjusted mean change from visit 2 (day 0) to the average value of available data during clinic visits.

Table 3: Changes from run-in in symptom control and lung function in patients using maintenance budesonide-formoterol plus alternative reliever medications

randomisation, additional increases in FEV$_1$ of 0·05 L and 0·08 L were seen with as-needed budesonide-formoterol versus formoterol (p=0·0001; figure 3) and terbutaline (p<0·0001). Mean morning PEF increased progressively from run-in in all groups, with a small additional improvement observed with as-needed budesonide-formoterol versus both formoterol (4·8 L per min; p=0·0040) and terbutaline (7·5 L per min; p<0·0001; table 3). These improvements were maintained during the study (webfigure). Similar improvements were noted with as-needed budesonide-formoterol for mean evening PEF compared with formoterol (5·4 L per min; p=0·0011) and terbutaline (6·3 L per min; p=0·0001) (table 3). There was no significant difference in morning or evening PEF between as-needed formoterol and terbutaline (table 3).

Use of reliever medication decreased over time in all groups, an effect that was maintained during the study (webfigure). The mean reliever use at run-in was 1·88 inhalations per day. During the treatment, this amount decreased to 1·02 inhalations per day in the budesonide-formoterol group and to 1·23 and 1·26 inhalations per day in the formoterol and terbutaline groups, respectively. Thus, the average additional dose of budesonide used by patients in the budesonide-formoterol group for maintenance and reliever therapy was 163 µg per day. Patients receiving budesonide-formoterol used fewer as-needed inhalations per day than those receiving formoterol or terbutaline (p<0·0001 for both; table 3) and on 52% of treatment days patients in the budesonide-formoterol group did not use any as-needed medication compared

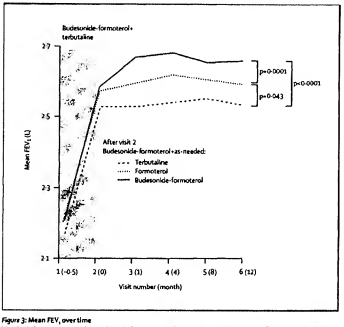

Figure 3: Mean FEV$_1$ over time
The shaded area represents the run-in period. Patients received maintenance budesonide-formoterol 160/4·5 µg, one inhalation twice daily, plus as-needed terbutaline during run-in. Post-randomisation, patients received budesonide-formoterol 160/4·5 µg 1 inhalation twice daily plus one of the following for as-needed relief: additional inhalations of budesonide-formoterol 160/4·5 µg; formoterol 4·5 µg; or terbutaline 0·4 mg. FEV$_1$=forced expiratory volume in 1 s.

	Number of patients with event (%)		
	Terbutaline as-needed group (n=1138)	Formoterol as-needed group (n=1137)	Budesonide-formoterol as-needed group (n=1107)
SAEs reported as asthma	26 (2%)	23 (2%)	16 (1%)
DAEs reported as asthma	10 (1%)	14 (1%)	1 (0·1%)
Pharmacologically predictable adverse events			
Tremor	2 (0·2%)	4 (0·4%)	1 (0·1%)
Palpitation/tachycardia	4 (0·4%)	6 (0·5%)	7 (0·6%)
Hoarseness	7 (0·6%)	11 (1%)	7 (0·6%)
Oral candidosis*	10 (1%)	11 (1%)	22 (2%)
Dysphonia	0 (0)	1 (0·1%)	0 (0)

SAE=serious adverse event. DAE=adverse event leading to discontinuation of the patient from the study. *Includes (all candidosis and any adverse event considered closely related to oral candidosis (ie, pharyngeal candidosis, oropharyngeltis fungal, or oral fungal infection).

Table 4: Adverse events reported as asthma and pharmacologically predictable adverse events

with 48% in both comparator groups. There was no significant difference in reliever use between the formoterol and terbutaline groups. In terms of weekly medication use, at run-in the median weekly as-needed reliever use (averaged over the past 10 days of run-in) was 10·5 inhalations, while during the treatment period the median as-needed use was 4·4 inhalations per week in the as-needed budesonide-formoterol group. The corresponding value for patients in the as-needed formoterol and terbutaline groups was 5·6 and 5·7 inhalations per week, respectively.

High usage of short-acting reliever is a risk factor for life-threatening asthma.[9] We thus did a post-hoc examination of patients with frequent high use of reliever therapy (arbitrarily defined as four or more as-needed inhalations on more than 300 study days (descriptive statistics only)). This pattern of high use was uncommon in all groups, being seen in 70 (6·3%) of 1107 patients in the as-needed budesonide-formoterol group, 111 (9·8%) of 1137 in the formoterol group, and 130 (11·4%) in the terbutaline group. The yearly rates per patient of severe exacerbations in outlying patients using as-needed budesonide-formoterol was 0·33, which was at least half the rate seen in outlying patients using formoterol (0·77) and terbutaline (0·76).

All treatments were well tolerated. The number of patients with non-fatal serious adverse events was comparable across groups: 70 (6·3%), 55 (4·8%), and 65 (5·7%) for the as-needed budesonide-formoterol, formoterol, and terbutaline groups, respectively. Serious adverse events reported as asthma occurred in 16, 23, and 26 patients in the budesonide-formoterol, formoterol, and terbutaline groups, respectively (table 4). Discontinuations due to asthma were less common in the as-needed budesonide-formoterol group compared with the formoterol and terbutaline groups (one patient versus 14 patients and 10 patients, respectively). There were four deaths during the study (one in the as-needed budesonide-formoterol group, one in the formoterol group, and two in the terbutaline group), but none was judged by the investigator to be causally related to the study drugs and none were reported as asthma. The incidence of pharmacologically predictable adverse events related to treatment with inhaled corticosteroids or β2 agonists was rare and comparable across all treatment groups (table 4).

Discussion

In this large, 12-month, double-blind study, we have shown that maintenance plus as-needed budesonide-formoterol reduced the risk of severe exacerbations and events resulting in emergency room visits or hospitalisations compared with maintenance budesonide-formoterol plus either formoterol or terbutaline as needed. Our study shows that the budesonide component of the budesonide-formoterol combination used when needed has a beneficial role in patients who remain symptomatic despite treatment with combination maintenance therapy.

As-needed formoterol (a rapid-acting and long-acting reliever therapy) was also seen to provide better exacerbation control compared with terbutaline. Therefore, the reduction in severe exacerbations can be attributed partly to the as-needed formoterol component of the combination. This finding extends the earlier results of Tattersfield and colleagues,[6] who reported a similar benefit with as-needed formoterol in patients using inhaled corticosteroids alone. However, the key finding in the present study is that the budesonide component of budesonide-formoterol as needed results in additional reductions in the overall rates of severe exacerbations and emergency room visits or hospitalisations of 33% and 27%, respectively, over formoterol as needed.

The low exacerbation rate (19 events in 100 patients per year) achieved with budesonide-formoterol for maintenance and reliever therapy in the present study was obtained with 320 μg per day of maintenance budesonide plus an additional steroid dose that could vary between 0 and 1600 μg per day, depending on the patient's need for reliever medication. Although additional daily doses up

to 1600 μg were allowed in the protocol, the actual use of high doses was rare: just four patients used an average dose (maintenance plus as-needed) above 1280 μg per day of budesonide. On more than half of the treatment days, no additional inhalations were used by the budesonide-formoterol maintenance and reliever therapy group, and the average additional dose of budesonide was only 163 μg per day.

Despite the modest budesonide dose used, the exacerbation rates reported here were at least as low as those previously reported in other 12-month efficacy studies in similar patient populations using higher fixed doses of inhaled corticosteroids plus LABA[1] or titration to higher fixed doses of inhaled corticosteroids, LABA, or both.[18] The 45% reduction in the risk of a severe exacerbation with as-needed budesonide-formoterol versus terbutaline was achieved with a small (50%) increase in corticosteroid dose, comparing favourably with the 14% reduction in exacerbation risk seen with a two-fold to four-fold (100–300%) increase in maintenance corticosteroids used in several controlled trials.[4] However, the fact that self-reported drug use was not corroborated by a more accurate assessment, eg, electronic compliance monitoring, is a limitation of the study that should be considered.

The current study was mainly an efficacy study and was not specifically powered to assess rare events such as asthma mortality. Asthma-related deaths and serious adverse events have been reported to increase with LABA therapy in populations where the use of inhaled corticosteroids was not mandatory.[19,20] However, the RELIEF study,[11] which was done in 18 124 asthma patients, showed no similar associations with as-needed formoterol compared with salbutamol. In the present study, there were no asthma deaths, and the incidence of asthma-related serious adverse events was highest in the terbutaline as needed group. Discontinuations due to asthma were low in all three groups, occurring in only one in 1113 patients treated with budesonide-formoterol as needed, a rate more than 10-fold lower than that seen in either the formoterol or terbutaline as needed groups. No drug-related serious adverse events were identified with this novel regimen, and pharmacologically predictable adverse events were similar in all three treatment groups. Although adrenal function tests were not done in the present study, results of two large 1-year studies have shown that maintenance plus reliever budesonide-formoterol has a similar effect on adrenal function as budesonide 800 μg per day in adults,[7,8,21] and 400 μg per day in children.[21]

The reduction in exacerbations seen with a modest average increase in the inhaled corticosteroid dose for the budesonide-formoterol maintenance and reliever regimen suggests that a crucial factor might be related to the timing of the inhaled corticosteroid dose. After inhalation of inhaled corticosteroids, lung tissue concentrations decline over time and within 6 h values might be less than 10% of peak values.[22] Therefore, inhaled corticosteroids taken as needed might supplement the tissue concentrations of inhaled corticosteroids at a time when the concentration of inhaled corticosteroids remaining from the scheduled maintenance dose is suboptimum. The significance of tissue kinetics is suggested by the finding that, in severe unstable asthma, increasing the dose frequency from two to four-times daily while maintaining the same total daily inhaled corticosteroids dose provided greater efficacy.[23] The mechanism of action of as-needed formoterol in preventing exacerbations is also uncertain. The benefit has been suggested to be due to a stabilising effect on airway smooth muscle during an exacerbation.[24] Others have suggested that higher doses of formoterol can reduce neutrophilic inflammation.[25] Interestingly, in steroid-dependent asthma patients with acute, viral-induced exacerbations, neutrophilia rather than eosinophilia is a defining feature of the acute event.[26]

Evidence from a European study of adults with asthma has indicated that patients recognise and respond to the early signs of an impending worsening by increasing their medication. However, patients were seen to increase their short-acting β2 agonist (SABA) at the expense of their anti-inflammatory treatment.[27] The use of budesonide-formoterol for maintenance and reliever therapy could enable supplementary doses of both budesonide and formoterol to be taken early in the course of an asthma worsening, avoiding over-reliance on SABA medication. Such a treatment regimen contrasts with other approaches that rely on a substantial worsening and a formalised action plan to direct dose increases.[6,28] In such cases, late intervention has provided mixed results. In one study, a temporary increase in the dose and dose frequency of budesonide, even if initiated late in the course of a worsening, was shown to reduce the need for oral corticosteroid therapy.[29] However, a late intervention with a double dose of inhaled corticosteroids alone has been shown to be ineffective.[29,30]

Improvements in lung function, symptom scores, night-time awakenings, and reliever use were consistently greater in patients treated with budesonide-formoterol for maintenance and reliever therapy compared with formoterol or terbutaline (table 3). The improved efficacy seen in the first month of treatment with as-needed budesonide-formoterol for these secondary outcome measures was sustained throughout the 12-months of treatment. Notably, although as-needed formoterol reduced the exacerbation rate compared with as-needed terbutaline, it did not reduce as-needed medication use or symptom-related variables. Thus, although additional as-needed formoterol reduced exacerbations, daily symptoms were not affected further by increases in the formoterol dose.

Despite the availability of effective maintenance therapy, objectively assessed asthma control in the community seldom approaches guideline targets, and

preventable exacerbations are all too frequently encountered. In the RELIEF study,[9] 28–43% of 8988 patients meeting the GINA criteria for Treatment Steps III and IV had at least one exacerbation during the 6-month study. Additionally, in an observational study done in the UK, 14–21% of 588 randomly selected patients starting combination therapy for the first time needed oral steroids in the first 6 months of treatment.[10] In our study, 8–14% of patients had an exacerbation during the first 6 months of treatment. This finding suggests that our results could have applicability to a large proportion of asthma patients suitable for combination therapy. Our findings should not be extrapolated to patients with intermittent asthma, however, or to those well controlled on inhaled corticosteroids alone. Patients poorly controlled on low-dose inhaled corticosteroids have shown striking improvements in daily control and a 76% reduction in exacerbations (as defined here) when using maintenance plus as-needed budesonide-formoterol compared with a higher dose of inhaled corticosteroids alone.[4] In the present study, patients were poorly controlled on low-dose inhaled corticosteroids and LABA therapy at randomisation. Although exacerbations were reduced, and asthma control improved with budesonide-formoterol as reliever compared with either of the alternative rapid-acting β2 agonists, there remained potential for further improvement in daily control. Thus we cannot exclude the possibility that, in our study population, increases in maintenance therapy could have further improved clinical outcomes. Consequently, before this approach can be widely adopted, examination will be needed as to whether this regimen is both more effective and cost-effective compared with a higher maintenance dose of inhaled corticosteroids and LABA with short-acting β2-agonist treatment on all aspects of asthma control.

So far, budesonide-formoterol maintenance and reliever therapy has only been compared with higher maintenance inhaled corticosteroids and LABA doses in an open-label study where clinicians were free to titrate the maintenance dose of inhaled corticosteroids and LABA, as occurs in traditional practice, in both study groups. In this setting, as-needed budesonide-formoterol was able to show improvements in asthma control and allow greater reductions in maintenance therapy compared with traditional combination therapy.[11]

As-needed formoterol provides increased protection from severe exacerbations, compared with terbutaline. Furthermore, the addition of as-needed inhaled corticosteroids (budesonide) to as-needed formoterol greatly enhances this protective effect. The results from this study provide insights into our understanding of how to use inhaled corticosteroids and LABA therapy optimally to prevent asthma exacerbations. Our findings also challenge the established use of maintenance therapy plus rapid-acting β2 agonistr as the only means of controlling asthma.

Contributors

All authors had unlimited access to the clinical study report and statistical analysis and contributed to the interpretation of the data. All authors were involved in every stage of manuscript preparation and the decision to submit the study article. Tito Atienza, Pál Magyar, and Umesh G Lalloo were clinical investigators in the study and contributed to the study supervision (Tito Atienza only), reviewing of the data, writing of the clinical study report, and patient recruitment. Carin Jorup and Per Larsson contributed to the study design, study planning, decisions taken during the study, writing of the statistical report/clinical trial report, interpretation of the results, and statistical analysis (Per Larsson only). All authors made final decisions on all aspects of the article and hence are in agreement with, and approve, the final version of the submitted article.

Conflict of interest statement

K Rabe has, within the last 5 years, received research funding, honoraria for lectures, and is a member of asthma advisory boards for AstraZeneca and GlaxoSmithKline. C Jorup (Senior Clinical Research Physician) and P Larsson (Statistical Science Director) are employed at AstraZeneca research and development, Lund, Sweden. U G Lalloo has been sponsored to attend an international scientific meeting by AstraZeneca. T Atienza and P Magyar declare no conflict of interest. AstraZeneca, Lund, Sweden, supported this study.

Acknowledgments

We thank the study investigators for their work in conducting the trial. We thank Annika B Jonsson (AstraZeneca, Lund, Sweden), who was the study team leader, Ian Naya, and Tomas LG Andersson (AstraZeneca, Lund, Sweden), who contributed to the interpretation of the results and the compilation of the manuscript, and Julie Young (Adelphi Communications Ltd) who provided medical writing support on behalf of AstraZeneca.

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CURRENT MEDICAL RESEARCH AND OPINION®
VOL. 20, NO. 9, 2004, 1403–1418

0300-7995
doi:10.1185/030079904X2051

Appendix C

ORIGINAL ARTICLE

Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma

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Key words: Asthma – Budesonide – Budesonide/formoterol – Exacerbations – Inhaled corticosteroids – Long-acting β_2-agonists – Single inhaler

SUMMARY

Objectives: This study evaluated the efficacy and safety of a novel asthma management strategy – budesonide/formoterol for both maintenance and symptom relief (Symbicort Single Inhaler Therapy*) – compared with a higher maintenance dose of budesonide in patients with moderate to severe asthma.

Methods: This was a 12-month, randomised, double-blind, parallel-group study. Symptomatic patients with asthma (n = 1890; mean age 43 years [range 11 years–80 years], mean baseline forced expiratory volume in 1 s [FEV_1] 70% of predicted, mean inhaled corticosteroid [ICS] dose 746 μg/day) received either budesonide (160 μg, 2 inhalations twice daily) plus terbutaline 0.4 mg as needed or a daily maintenance dose of budesonide/formoterol (160/4.5 μg, 2 inhalations once daily) with additional inhalations of budesonide/formoterol 160/4.5 μg as needed. Time to first severe exacerbation (hospitalisation/emergency room [ER] treatment or systemic steroids due to asthma worsening or a fall in morning peak expiratory flow [PEF] to ≤ 70% of baseline on 2 consecutive days) was the primary outcome variable.

Results: A total of 1890 patients were randomised, of whom 1563 (83%) had severe

* Symbicort Single Inhaler Therapy is a trademark owned by the AstraZeneca group

asthma. The time to first severe exacerbation was prolonged by budesonide/formoterol single inhaler therapy ($p < 0.001$) compared with a higher dose of budesonide. The risk of having a severe exacerbation was 39% lower with budesonide/formoterol single inhaler therapy compared with budesonide ($p < 0.001$). The number needed to treat to prevent one severe exacerbation per year with budesonide/formoterol compared with budesonide was 5. The budesonide/formoterol group had 45% fewer severe exacerbations requiring medical intervention per patient compared with the budesonide group ($p < 0.001$). Budesonide/formoterol patients had fewer hospitalisations/ER treatments (15 vs 25 events, respectively [descriptive statistics]) and fewer treatment days with systemic steroids (1776 days vs 3177 days, respectively [descriptive statistics]) compared with budesonide patients. Budesonide/formoterol single inhaler therapy patients used less as-needed medication compared with budesonide patients (0.90 vs 1.42 inhalations/day; $p < 0.001$). The mean daily ICS dose was lower in the budesonide/formoterol group than in the budesonide group (466 μg/day vs 640 μg/day). Over the 12-month study period, the budesonide/formoterol group achieved asthma control sufficient to not require any additional as-needed medication on 60% of days. Overall, budesonide/formoterol single inhaler therapy gave 31 more asthma control days (a night and day with no asthma symptoms and no as-needed medication use) per patient-year and 12 additional undisturbed nights per patient-year compared with a higher dose of budesonide. Both treatments were well tolerated.

Conclusion: Budesonide/formoterol single inhaler therapy has the potential to provide a complete asthma management approach with one inhaler, demonstrating a high level of efficacy in patients with moderate to severe asthma.

Introduction

Despite the availability of international asthma guidelines and effective anti-inflammatory and bronchodilator medications, many patients continue to suffer from poorly controlled asthma[1]. This is partly due to poor adherence to inhaled corticosteroid (ICS) therapy, as patients often over-rely on their short-acting β_2-agonist reliever medication in order to achieve rapid relief from symptoms, at the expense of their daily maintenance therapy. Consequently, the underlying inflammation associated with asthma may be undertreated, allowing symptoms to escalate further and increasing the risk of exacerbations. Evidence suggests that the use of multiple inhalers for daily maintenance therapy and reliever medication also contributes to poor adherence to asthma treatment[2].

The introduction of single inhalers combining an ICS with a long-acting β_2-agonist represents a key development in asthma management. There are currently two products available: budesonide/formoterol (Symbicort Turbuhaler*) and salmeterol/fluticasone (Seretide Diskus†). Both budesonide/formoterol and salmeterol/fluticasone are usually administered via fixed dosing regimens, whereby patients receive a fixed daily maintenance dose of medication and have a separate inhaler containing reliever medication for as-needed relief from symptoms. An alternative treatment strategy, developed for budesonide/formoterol, involves patients adjusting the maintenance dose in response to their current level of asthma control (referred to as adjustable maintenance dosing) – increasing the dose during periods of worsening asthma and reducing it when control is achieved. This ensures that the minimum effective dose of ICS is used to maintain control in line with guideline recommendations[3].

Studies comparing both fixed and adjustable maintenance dosing regimens with budesonide/formoterol demonstrated that adjustable maintenance dosing provides superior efficacy with a lower overall steroid load compared with traditional asthmatherapy[4,5]. Budesonide/formoterol adjustable maintenance dosing has also been compared with fixed-dose salmeterol/fluticasone in patients with moderate to severe asthma[6]. In this study, patients received either fixed dosing with budesonide/formoterol or salmeterol/fluticasone or adjustable maintenance dosing with budesonide/formoterol[6], with all patients using a short-acting β_2-agonist as reliever medication. Patients in the adjustable maintenance dosing group received a written self-management plan stipulating the course of action to take in the event of asthma worsening. Adjustable maintenance dosing with budesonide/formoterol provided more effective asthma control, reducing the rate of severe exacerbations by 40% compared with fixed-dose salmeterol/fluticasone ($p = 0.018$)[6]. Budesonide/formoterol adjustable maintenance dosing and fixed dosing treatment were equally well tolerated[4-6].

Evidence suggests, however, that written action plans are not widely used in practice[7,8]. In addition, action plans often advise patients to step up treatment after

* Symbicort and Turbuhaler are registered trademarks owned by the AstraZeneca group
† Seretide and Diskus are trademarks of the GlaxoSmithKline group

2 days of awakenings, increased reliever use or falls in peak expiratory flow (PEF), thus introducing a time lag between an asthma worsening and increasing medication, which could reduce the effectiveness of this approach. Furthermore, action plans can involve different treatment regimens with multiple inhalers, which may introduce an element of complexity and impact on patient adherence[9].

We hypothesised that using a novel asthma treatment strategy with a combination inhaler for both maintenance and relief in patients with moderate to severe asthma would provide more effective asthma control compared with a traditional fixed dosing regimen. With this strategy – budesonide/formoterol single inhaler therapy – patients receive a low daily dose of budesonide/formoterol for maintenance therapy and take additional doses as needed for symptom relief. Importantly, patients do not need a separate inhaler for reliever medication with budesonide/formoterol single inhaler therapy because formoterol has an onset of action as fast as salbutamol, 1–3 min after inhalation[10,11]. Indeed, studies have shown that formoterol[12,13] and budesonide/formoterol[14] are as effective as salbutamol in providing relief from severe acute bronchospasm in patients presenting to an emergency room (ER). Furthermore, the efficacy and tolerability of as-needed formoterol have been demonstrated in a large randomised study involving 18 000 patients[15]. In this study, formoterol as needed reduced exacerbations when used in addition to maintenance therapy with either ICS or ICS plus a long-acting β_2-agonist[15].

As budesonide/formoterol single inhaler therapy delivers both maintenance therapy and as-needed medication, it has the potential to provide a complete management strategy with one inhaler, therefore simplifying asthma therapy. A key advantage of budesonide/formoterol single inhaler therapy compared with both fixed and adjustable dosing regimens is that patients can easily adjust their medication immediately, at the onset of symptoms, by taking additional inhalations as needed. Consequently, budesonide/formoterol single inhaler therapy can provide timely increases in both anti-inflammatory and bronchodilator medications, thereby preventing undertreatment and reducing the risk of exacerbations and periods with poor symptom control.

The efficacy of budesonide/formoterol single inhaler therapy has been demonstrated previously in a 6-month study in patients with mild to moderate asthma[16]. In the current study, we compared the efficacy and safety of budesonide/formoterol single inhaler therapy (160/4.5 µg 2 inhalations once daily plus additional doses as needed) with a higher maintenance dose of budesonide alone (160 µg 2 inhalations twice daily) plus terbutaline as needed in patients with moderate to severe asthma, over 12 months.

Patients and methods

This randomised, double-blind, double-dummy, active-controlled study with a parallel-group design was conducted in 211 centres in the following countries: Argentina, Australia, Canada, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Mexico, The Netherlands, New Zealand, Norway, Portugal, Russia, South Africa and Turkey. The first patient was enrolled on 23 May 2001, with the last patient completing the study on 22 January 2003. All patients were outpatients recruited from hospital or primary care settings. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and local regulations, each study centre having received ethical approval of the protocol prior to study commencement. All patients and parents/guardians of patients aged < 18 years were required to give written informed consent before any study-related procedures were performed.

Study Design

Male and female patients aged 12 years–80 years with a diagnosis of asthma (as defined by the American Thoracic Society[17]) for at least 6 months were eligible for inclusion in the study if they had: (i) a history of ≥ 1 clinically important asthma exacerbations as judged by the investigator 1 month–12 months prior to study entry (Visit 1); (ii) used ICS (any brand) at a dose of 400 µg/day–1600 µg/day for at least 3 months and at a constant dose for at least 30 days prior to study entry; (iii) a forced expiratory volume in 1 s (FEV_1) 50%–90% of predicted normal; (iv) ≥ 12% reversibility in increase from baseline FEV_1 15 min after inhalation of terbutaline sulphate 1 mg (Bricanyl Turbuhaler; AstraZeneca, Sweden). Additionally, for patients aged ≥ 18 years, an increase in baseline FEV_1 of ≥ 200 mL within 15 min of inhalation of terbutaline was required at study entry. Patients were excluded from the study if they had received systemic steroids or inhaled cromones within 30 days of study entry; if they had taken ≥ 3 courses of systemic steroids in the last 6 months; if they had cardiovascular disease or other significant disorders; if they had experienced a respiratory tract infection affecting asthma in the last 30 days; or if they were smokers with a smoking history of > 10 pack-years.

Patients completed a 2-week run-in period to collect baseline data, during which they continued to use their regular dose of ICS and took inhalations of terbutaline 0.5 mg (metered dose corresponding to a delivered dose of 0.4 mg) (Bricanyl; AstraZeneca, Sweden) as needed administered via a Turbuhaler. Patients were only eligible for randomisation if they were symptomatic and had moderate to severe asthma based on their level of

treatment and a history of clinically important exacerbations. Patients were not eligible if they had taken more than 10 inhalations of as-needed medication on any day during run-in.

All eligible patients were randomised to 12 months' treatment with either budesonide/formoterol single inhaler therapy 160/4.5 μg (Symbicort; AstraZeneca, Sweden) 2 inhalations once daily in the evening with additional inhalations as needed, or budesonide 160 μg (Pulmicort; AstraZeneca, Sweden) 2 inhalations twice daily in the morning and evening plus terbutaline 0.4 mg as needed. All study drugs were administered via Turbuhaler as delivered doses (a delivered dose of 160 μg budesonide corresponds to a metered dose of 200 μg and a delivered dose of 4.5 μg formoterol corresponds to a metered dose of 6 μg). Patients were not instructed to rinse their mouth with water following inhalation of the study drugs. Patients were allowed to take a maximum of 10 as-needed inhalations of either budesonide/formoterol or terbutaline per day. If > 10 inhalations were required in a single day, patients were asked to contact the investigator for reassessment.

Exacerbation Treatment

All severe exacerbations were to be treated with a 10-day course of oral prednisolone 30 mg/day. If the patient needed > 10 days of treatment with prednisolone, the 11th day of treatment was considered to be the start of a second severe exacerbation. A deterioration of asthma resulting in the need for 3 courses of systemic steroids during 3 months, or a total of 5 courses during the study, led to the patient being withdrawn.

Blinding and Randomisation

To ensure treatment blinding, a double-dummy design was employed so that each patient received three identical Turbuhalers (labelled as inhaler 1, 2 or 3). Patients were instructed to take 2 inhalations from inhaler No. 1 (containing budesonide or placebo for patients in the single inhaler therapy group) every morning upon rising and 2 inhalations of inhaler No. 2 (containing budesonide or budesonide/formoterol) every evening before going to bed. Inhaler No. 3 (containing treatment-specific reliever medication – budesonide/formoterol or terbutaline) could be used as needed when patients experienced asthma symptoms.

The randomisation code was prepared at the sponsor's site by a person not involved in the analysis of data. Computerised randomisation of treatment was performed using the computer program RandLink. Patients were randomised in balanced blocks sequentially according to their enrolment code. Treatment codes were not broken until all decisions on the availability of patient data had been made, except in the case of medical emergencies.

Efficacy Evaluations

The primary outcome variable was time to first severe exacerbation. A severe exacerbation was defined as asthma worsening resulting in hospitalisation or ER treatment, the need for systemic steroids, or a fall in morning PEF to ≤ 70% of baseline on 2 consecutive days. Severe exacerbations that required medical intervention (hospitalisation/ER treatment or systemic steroids) were also analysed. A mild exacerbation day was defined as asthma worsening resulting in either: night-time awakening(s), a ≥ 20% decrease in morning PEF from baseline or an increase of ≥ 2 inhalations of reliever medication over a 24-h period compared with baseline. A mild exacerbation was defined as two consecutive mild exacerbation days of the same type (listed above).

PEF measurements were performed by the patient using a Mini-Wright peak flow meter (Clement Clark, Harlow, UK), following careful instruction, and were recorded on diary cards. Spirometric measurements were performed at all clinic visits within ± 1 h of the time of the first reading at baseline (randomisation; Visit 2), usually between 07:00 and 10:00, and in accordance with the European Respiratory Society recommendations[18].

Daytime and night-time asthma symptoms were recorded by patients on diary cards, graded on a scale of 0–3 (0 = no symptoms; 1 = aware of asthma symptoms but can easily tolerate them; 2 = asthma causing enough discomfort to cause problems with normal activities/sleep; 3 = unable to do normal activities/sleep because of asthma). These scores were summed to calculate the total daily asthma symptom score (scale of 0–6). Patients also recorded night-time awakenings due to asthma symptoms. Each morning and evening, patients recorded the number of inhalations of maintenance and as-needed medication taken. The percentage of symptom-free days (defined as a night and a day with no asthma symptoms and no night-time awakenings due to asthma) and the percentage of reliever medication-free days (defined as a day and a night with no reliever medication use) were calculated from diary card data, to provide an overall measure of symptom control. These endpoints were combined to determine the percentage of asthma-control days (defined as a night and a day with no asthma symptoms and no intake of reliever medication, and a night with no awakenings due to asthma symptoms).

Clinical Safety Assessments

The incidence and intensity of adverse events were recorded at all clinic visits during the treatment period. Adverse events and serious adverse events were reported spontaneously or observed and recorded in

response to a standard question asked by the investigator: 'Have you had any health-related problems since the previous visit?'

Routine laboratory assessments and morning plasma (p)-cortisol analysis were performed in a subgroup of patients at baseline and after 6 months and 12 months of treatment. An adrenocorticotropic hormone (ACTH) stimulation test was also performed to assess adrenal function at baseline and after 12 months of treatment. p-cortisol concentrations were analysed using a gas chromatography and mass spectrometry method with the lower limit of quantification at 20 nmol/L, as described by Hsu *et al.*[19]. Vital signs and electrocardiogram measurements were also assessed.

Statistical Analysis

All efficacy analyses were performed using intent to treat analysis on all randomised patients with data available after randomisation. All hypothesis testing was done using two-sided alternative hypotheses and p-values $< 5\%$ were considered statistically significant. Time to first severe exacerbation – the primary outcome variable – was compared between treatment groups using a log-rank test and a Cox proportional hazards model was used to compare treatments and calculate instantaneous risk. Assuming the true incidence of severe asthma exacerbations was 25% in one treatment group, in order to have an 80% probability of detecting a 19.2% reduction in incidence of severe exacerbations in the other treatment group (at the two-sided 5% level) a sample size of $n = 800$ per group was required. Time to first severe exacerbation requiring medical intervention and time to first mild exacerbation were also analysed as described above.

The total number of severe exacerbations requiring medical intervention (i.e. excluding PEF falls not recorded as severe exacerbations) and mild exacerbation days were compared between groups using a Poisson regression model. Confidence intervals (CIs) and p-values were adjusted for overdispersion. For all patient diary card variables and the percentage of mild exacerbation days, analysis was performed in terms of change from baseline. Baseline was defined as the average over the last 10 days of run-in and treatment as the average of all available data over the entire treatment period (excluding data from the day of randomisation). For FEV_1, baseline was the value measured at randomisation (Visit 2) and treatment was the mean of the available data from Visits 3–7. Changes from baseline were analysed by analysis of variance (ANOVA), with treatment and country as fixed factors and the baseline value as a covariate. The adjusted mean change from run-in was obtained from the analysis model and treatment differences and 95% CIs were calculated.

The change in morning p-cortisol from baseline (Visit 2) to end of treatment (Visit 7) was compared between treatment groups using a multiplicative (log transformation of data) ANOVA. For ACTH-stimulated p-cortisol, both the maximal p-cortisol after stimulation and the increase in p-cortisol from pre- to post-test were compared between treatments. A multiplicative ANOVA model was used to assess the change in maximal p-cortisol after ACTH stimulation; an additive ANOVA was performed to assess any increase in p-cortisol from before to after the test.

Results

From a total of 2089 patients enrolled in the study, 1890 patients were randomised to treatment with either budesonide/formoterol single inhaler therapy ($n = 947$) or a higher maintenance dose of budesonide alone ($n = 943$) (Figure 1). All randomised patients were included in the 12-month efficacy and safety analysis ($n = 1890$). During the study, 397 protocol deviations were reported involving a total of 306 patients. The most common protocol deviation was randomisation in error, with a total of 80 patients (4%) reported to have at least one deviation of this nature (43 patients in the budesonide/formoterol group and 37 patients in the budesonide group). No protocol violation occurring during the study justified the exclusion of patients' data from the analysis.

Baseline characteristics were comparable between the treatment groups (Table 1). At baseline, 45% of patients in the budesonide/formoterol group and 44% of patients in the budesonide group were already using ICS plus a long-acting β_2-agonist or ICS/long-acting β_2-agonist combinations (Table 1). Of the 1890 patients randomised, the majority (1563 patients [83%]) were classified as having severe asthma according to modified Global Initiative for Asthma (GINA) guidelines[3]. Self-reported adherence to study medication was high (99%) and similar for both treatment groups.

Severe Exacerbations

The time to first severe exacerbation was significantly prolonged by treatment with budesonide/formoterol single inhaler therapy compared with a higher dose of budesonide ($p < 0.001$). The instantaneous risk of having a severe exacerbation was 39% lower for patients receiving budesonide/formoterol than for those treated with budesonide ($p < 0.001$) and fewer patients in this group experienced a severe exacerbation compared with the budesonide group (170 vs 259 patients, respectively) (Table 2). The reductions in all types of severe exacerbations are shown in Figure 2.

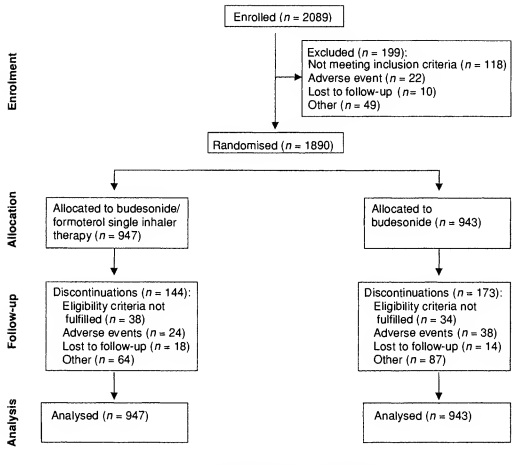

Figure 1. Patient flow during the study. Patients received either budesonide/formoterol single inhaler therapy (budesonide/formoterol 160/4.5 μg 2 inhalations once daily plus additional inhalations as needed) or budesonide 160 μg 2 inhalations twice daily plus terbutaline 0.4 mg as needed for 12 months

Table 1. Baseline clinical characteristics of patients

Characteristic*	BUD/FORM (n = 947)	BUD + SABA (n = 943)
Male/female	393/554	405/538
Age, years (range)	43 (12–79)	43 (11–80)
Asthma duration, years (range)	12 (1–65)	12 (1–71)
FEV_1 % predicted normal (range)†	70 (46–102)	70 (37–95)
FEV_1, % reversibility†	24 (7–152)	24 (7–171)
ICS dose at entry, μg (range)†	744‡ (250–2000)	748‡(400–2000)
Asthma medication at study entry, *n* (%)		
inhaled long-acting β_2-agonists	328 (35)	328 (35)
combination of inhaled long-acting β_2-agonists and ICS	95 (10)	83 (9)
Reliever use, number of inhalations/day (range)	1.9 (0.0–15.6)	2.0 (0.0–9.2)
Asthma symptom score, scale 0–6 (range)	1.8 (0.0–6.0)	1.9 (0.0–6.0)
Symptom-free days, % (range)	10 (0–100)	10 (0–100)
Asthma-control days, % (range)	8 (0–100)	8 (0–90)

*All values are presented as absolute numbers or as mean (range), except asthma duration (median)

†Range indicates some patients in the intention to treat population had minor deviations in inclusion criteria that did not result in exclusion

‡Expressed as metered dose. A metered dose of 744 μg is equivalent to a delivered dose of 595 μg and a metered dose of 748 μg is equivalent to a delivered dose of 598 μg

BUD = budesonide; FEV_1 = forced expiratory volume in 1 s; FORM = formoterol; ICS = inhaled corticosteroid; SABA = short-acting β_2-agonist

Table 2. Primary outcome analysis of patients

Exacerbation	Number (%) of patients with event		Instantaneous risk of first exacerbation (hazard ratio; 95% CI)
	BUD/FORM (n = 947)	BUD + SABA (n = 943)	
All severe exacerbations	170 (18)	259 (27)	0.61 (0.50, 0.74)*
Severe exacerbations requiring medical intervention	137 (14)	212 (22)	0.61 (0.49, 0.75)*

*Between-group difference: $p < 0.001$
BUD = budesonide; CI = confidence interval; FORM = formoterol; SABA = short-acting β_2-agonist

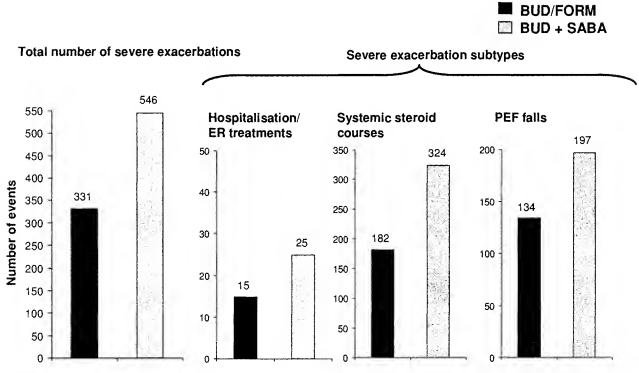

Figure 2. Severe exacerbations by type. A severe exacerbation was defined as asthma worsening resulting in hospitalisation/emergency room (ER) treatment; treatment with systemic steroids or a fall in morning peak expiratory flow (PEF) to ≤ 70% of baseline on 2 consecutive days. The total number of severe exacerbations is the sum of all exacerbations due to PEF falls, systemic steroid courses and hospitalisation/ER treatments. Patients received either budesonide/formoterol single inhaler therapy (budesonide/formoterol 160/4.5 μg 2 inhalations once daily plus additional inhalations as needed) or budesonide 160 μg 2 inhalations twice daily plus terbutaline 0.4 mg as needed for 12 months. BUD, budesonide; FORM, formoterol; SABA, short-acting β_2-agonist

Budesonide/formoterol single inhaler therapy resulted in fewer hospitalisations/ER treatments during the study compared with the budesonide group (15 vs 25 events, respectively [descriptive statistics]) (Figure 2). Patients receiving budesonide/formoterol single inhaler therapy required 142 fewer courses of systemic steroids compared with those receiving budesonide (182 vs 324 courses, respectively [descriptive statistics]) (Figure 2). A high proportion of exacerbations were defined by the PEF fall criterion in patient diaries (331 events) but were not recorded as severe exacerbations by the investigator: only 30 such events (9%) recorded in patient diaries were included in the case report forms by the investigator as confirmed exacerbations requiring treatment. When these untreated exacerbations were excluded from the analysis, budesonide/formoterol single inhaler therapy still increased the time to first severe exacerbation requiring medical intervention compared with budesonide (with an identical reduction in instantaneous risk [39%; $p < 0.001$]) (Table 2). The rate of severe exacerbations requiring medical intervention/patient was reduced by 45% with budesonide/formoterol single inhaler therapy compared

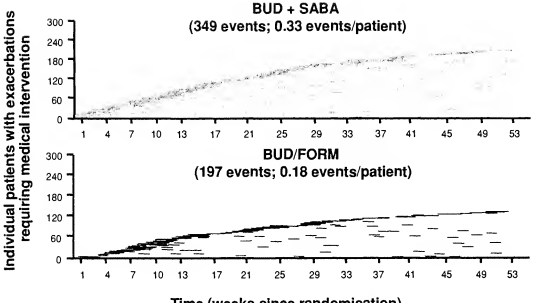

Figure 3. Total number of severe exacerbations requiring medical intervention over time for individual patients during the 12-month treatment period. The x-axis represents time and each number on the y-axis represents an individual patient. Each single line (——) represents one exacerbation for an individual patient. Exacerbations > 10 days in duration were considered as multiple events. Individual patients with > 1 exacerbation are shown as broken or extended lines in the same horizontal position. Patients received treatment with budesonide/formoterol single inhaler therapy (budesonide/formoterol 160/4.5 μg 2 inhalations once daily plus additional inhalations as needed) or budesonide 160 μg 2 inhalations twice daily plus terbutaline 0.4 mg as needed. The rate of severe exacerbations requiring medical intervention/patient was reduced by 45% with budesonide/formoterol single inhaler therapy vs budesonide (95% confidence intervals [CI]: 34%–54%; p < 0.001). BUD, budesonide; FORM, formoterol; SABA, short-acting β_2-agonist

with budesonide (95% CI: 34%–54%; $p < 0.001$). The total number of individual severe exacerbations requiring medical intervention over 12 months was reduced by 152 with budesonide/formoterol single inhaler therapy (first and repeated events totalled 197 events in the budesonide/formoterol group vs 349 events in the budesonide group) (Figure 3).

The number needed to treat (NNT) to avoid 1 exacerbation over 1 year with budesonide/formoterol single inhaler therapy vs budesonide was 5. Therefore, for every 100 patients treated with budesonide/formoterol single inhaler therapy for 1 year, there would be 20 fewer severe exacerbations requiring medical intervention compared with budesonide.

The severity of the exacerbations was further explored using mean profiles of diary card variables during severe exacerbations. Specifically, daily symptom scores, as-needed medication use/day and daily morning PEF were assessed for the period from 14 days before until 14 days after the start of each severe exacerbation. These profiles revealed generally lower symptom levels, lower as-needed medication use and higher PEF values for patients receiving budesonide/formoterol single inhaler therapy compared with those receiving budesonide.

Mild Exacerbations

Patients in the budesonide/formoterol group had a significantly longer time to first mild exacerbation compared with the budesonide group ($p < 0.001$). The instantaneous risk of experiencing a mild exacerbation was 32% lower with budesonide/formoterol treatment compared with fixed dosing with budesonide (95% CI: 25%–39%; $p < 0.001$). Budesonide/formoterol reduced the percentage of mild exacerbation days by 6.5% compared with budesonide (95% CI: –8.54, –4.39; $p < 0.001$).

Symptoms and Reliever Medication Use

Patients receiving budesonide/formoterol for both maintenance and symptom relief had significantly lower daytime and night-time asthma symptom scores compared with those receiving budesonide and as-needed terbutaline (Table 3), resulting in a lower total symptom score (Figure 4a). The percentage of nights with awakenings was significantly reduced with budesonide/formoterol ($p < 0.001$; Table 3), resulting in 12 fewer nights with awakenings/patient-year compared with budesonide. In addition, patients in the

Table 3. *Mean patient diary card variables*

Efficacy variable	BUD/FORM (n = 947)		BUD + SABA (n = 943)			
	Baseline* mean (range)	Treatment mean (range)	Baseline* mean (range)	Treatment mean (range)	Between-group difference† (95% CI)	p-value
Morning PEF, L/min	339.2 (77–670)	372.1 (100–751)	335.8 (104–749)	348.5 (93–805)	20.3 (16.5, 24.1)	< 0.001
Evening PEF, L/min	349.0 (77–722)	369.6 (99–720)	348.1 (101–718)	354.7 (91–808)	14.0 (10.4, 17.5)	< 0.001
Daytime asthma symptom score (0–3)	1.09 (0.0–3.0)	0.66 (0.0–3.0)	1.11 (0.0–3.0)	0.77 (0.0–3.0)	–0.10 (–0.14, –0.06)	< 0.001
Night-time asthma symptom score (0–3)	0.75 (0.0–3.0)	0.42 (0.0–3.0)	0.79 (0.0–3.0)	0.55 (0.0–3.0)	–0.11 (–0.15, –0.07)	< 0.001
Total asthma symptom score (0–6)‡	1.84 (0.0–6.0)	1.08 (0.0–6.0)	1.90 (0.0–6.0)	1.32 (0.0–6.0)	–0.21 (–0.28, –0.13)	< 0.001
Night-time awakenings (%)	22.6 (0–100)	9.4 (0–100)	23.5 (0–100)	13.0 (0–100)	–3.3 (–4.8, –1.7)	< 0.001
Symptom-free days (%)§	9.8 (0–100)	41.7 (0–100)	9.7 (0–100)	34.0 (0–100)	7.5 (4.5, 10.4)	< 0.001
As-needed free days (%)¶	29.3 (0–100)	59.8 (0–100)	26.3 (0–100)	47.2 (0–100)	11 (8.2, 13.8)	< 0.001
Asthma-control days (%)**	7.9 (0–100)	38.3 (0–100)	7.5 (0–90)	29.3 (0–100)	8.6 (5.7, 11.4)	< 0.001

*Mean of last 10 days of run-in
†From ANOVA model
‡Sum of the mean daytime and night-time scores
§A night and day with no symptoms and no asthma-related night-time awakenings
¶A night and day with no use of as-needed medication
**A night and day with no symptoms (night or day), no use of reliever medication and no asthma-related night-time awakenings
BUD = budesonide; CI = confidence interval; FORM = formoterol; PEF = peak expiratory flow; SABA = short-acting β_2-agonist

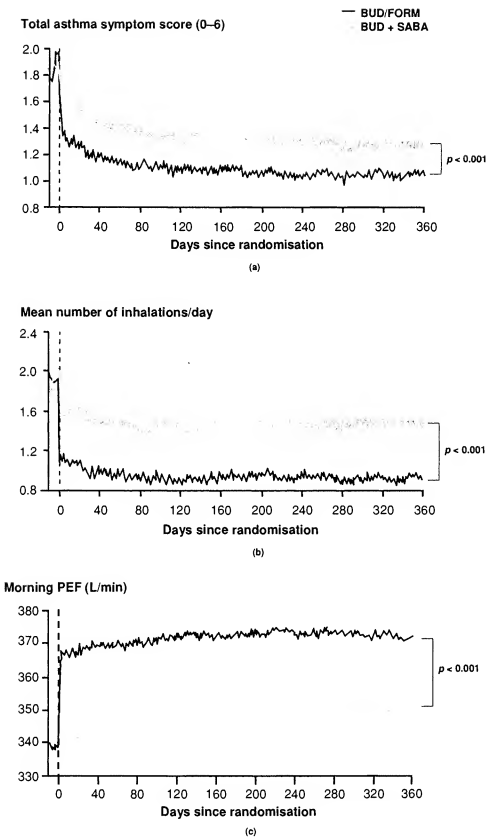

Figure 4. Diary card data over 12 months' treatment with either budesonide/formoterol single inhaler therapy (budesonide/formoterol 160/4.5 μg 2 inhalations once daily plus additional inhalations as needed) or budesonide 160 μg 2 inhalations twice daily plus terbutaline 0.4 mg as needed. Analysis was performed on change from run-in over the whole treatment period. (a) Mean total asthma symptom score (i.e. sum of daytime and night-time scores) (each scale ranged from 0 = no symptoms to 3 = unable to do normal activities [or sleep] because of asthma); (b) mean daily as-needed medication use per 24 h and (c) mean morning peak expiratory flow (PEF). BUD, budesonide; FORM, formoterol; SABA, short-acting β_2-agonist

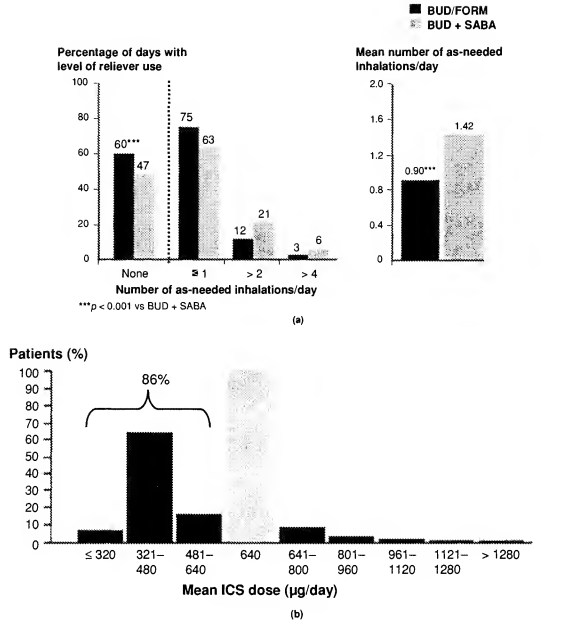

Figure 5. (a) Proportion of days with different levels of as-needed medication use (left panel) and mean overall daily use (right panel) and (b) overall distribution of mean daily inhaled corticosteroid use in patients treated with either budesonide/formoterol single inhaler therapy (budesonide/formoterol 160/4.5 µg 2 inhalations once daily plus additional inhalations as needed) or budesonide 160 µg 2 inhalations twice daily plus terbutaline 0.4 mg as needed. BUD, budesonide; FORM, formoterol; ICS, inhaled corticosteroid; SABA, short-acting β_2-agonist

budesonide/formoterol group had significantly more symptom-free days ($p < 0.001$; Table 3) – corresponding to an additional 27 days/patient-year – compared with the budesonide group. Treatment with budesonide/formoterol also resulted in significantly more asthma-control days ($p < 0.001$; Table 3), providing 31 more days/patient-year free from asthma symptoms, night-time awakenings and reliever medication use, compared with budesonide.

Patients in the budesonide/formoterol single inhaler therapy group used significantly less as-needed medication/day compared with the budesonide group during the treatment period (0.90 vs 1.42 inhalations/day, respectively; $p < 0.001$). As-needed medication use declined slightly during the initial months of the study in both treatment groups before stabilising (Figure 4b). Treatment with budesonide/formoterol single inhaler therapy resulted in significantly more reliever-free days compared with a higher maintenance dose of budesonide ($p < 0.001$; Table 3). Once-daily maintenance dosing with budesonide/formoterol, without additional as-needed inhalations, was achieved on 60% of days, while

Table 4. Incidence of pharmacologically predictable adverse events [number (%)]

Adverse event	BUD/FORM (n = 947)	BUD + SABA (n = 943)
Palpitation, tremor or tachycardia*	16 (2)	13 (1)
Dysphonia†	23 (2)	17 (2)
Candidiasis†	11 (1)	13 (1)

*Adverse events frequently related to treatment with β_2-agonists
†Adverse events frequently related to treatment with ICS
BUD = budesonide; FORM = formoterol; ICS = inhaled corticosteroids; SABA = short-acting β_2-agonist

patients receiving budesonide twice daily did not use as-needed medication on 47% of days (between-group difference $p < 0.001$) (Figure 5a). The proportion of days during which patients used > 2 or > 4 as-needed inhalations in any one day was approximately twice as common with budesonide plus as-needed terbutaline (21% and 6% of days, respectively) compared with budesonide/formoterol single inhaler therapy (12% and 3% of days, respectively) (Figure 5a).

Overall, there was no evidence of overuse of reliever medication in the budesonide/formoterol single inhaler therapy group. Patients receiving budesonide/formoterol and budesonide plus as-needed terbutaline used > 10 inhalations of as-needed medication on 0.1% and 0.2% of days during the study, respectively, with only 22 patients in the budesonide/formoterol group using > 10 inhalations in any one day compared with 67 patients in the budesonide group.

Total Steroid Dose

Patients using budesonide/formoterol for both maintenance and relief had a lower mean daily dose of ICS compared with those in the traditional fixed dosing group (466 μg/day vs 640 μg/day, respectively). The majority of patients in the budesonide/formoterol group (86%) had a mean daily ICS intake that was either equal to or lower than the maintenance dose of ICS used by patients in the budesonide group (640 μg) (Figure 5b). Additionally, patients in the budesonide/formoterol group needed 44% fewer treatment days with systemic steroids compared with the budesonide group (1776 vs 3177 treatment days, respectively [descriptive statistics]).

Lung Function

Budesonide/formoterol single inhaler therapy resulted in a significantly greater increase in morning PEF compared with fixed dosing with budesonide (mean difference: 20.3 L/min; $p < 0.001$ [Table 3]). The large increase in morning PEF observed in patients treated with budesonide/formoterol was apparent from the start of treatment and was maintained throughout the 12-month treatment period (Figure 4c). Similarly, patients in the budesonide/formoterol group had significantly greater increases in evening PEF compared with those receiving budesonide (Table 3). Improvements in FEV_1 were significantly greater in patients receiving budesonide/formoterol single inhaler therapy compared with those receiving budesonide (treatment means were 2.54 L vs 2.45 L, respectively; mean difference: 0.10 L [95% CI: 0.071, 0.130; $p < 0.001$]).

Safety

The incidence, frequency and profile of adverse events, and days of exposure to the investigational product were similar between treatment groups, with a total of 526/947 patients (56%) in the budesonide/formoterol group experiencing an adverse event compared with 533/943 patients (57%) in the budesonide group. Both treatments were well tolerated and adverse events were mainly mild to moderate in intensity. The most commonly reported adverse events in the budesonide/formoterol and budesonide groups were respiratory infection (172 [18%] vs 177 [19%] patients, respectively), bronchitis (63 [7%] vs 72 [8%] patients, respectively) and aggravated asthma (28 [3%] vs 43 [5%] patients, respectively). The incidence of adverse events related to ICS or β_2-agonists was low and similar between treatment groups (Table 4). A total of 113 serious adverse events were reported: 58 in the budesonide/formoterol single inhaler therapy group and 55 in the budesonide group. Two serious adverse events (atrial fibrillation and dizziness) – both in the budesonide/formoterol group – were considered by the investigator to be causally related to the investigational

product. Fewer patients in the budesonide/formoterol group discontinued the study as a result of adverse events (24 patients [3%] vs 38 patients [4%] in the budesonide group). Three deaths were reported during the study – one in the budesonide/formoterol group (peritoneal metastases) and two in the budesonide group (myocardial infarction and hypertrophic cardiomyopathy). None of these was judged to be causally related to the investigational products or directly related to asthma.

No clinically important differences were observed between treatment groups or over time during the 12-month treatment period for any of the laboratory variables studied. Mean morning p-cortisol concentrations remained stable over the study duration in both groups: 310 nmol/L at baseline and 306 nmol/L at the end of treatment with budesonide/formoterol vs 278 nmol/L at baseline and 254 nmol/L at the end of treatment with budesonide (mean ratio from baseline to end of treatment was 15% higher with budesonide/formoterol vs budesonide ($p = 0.06$). No statistically significant difference was observed between treatment groups for mean maximal p-cortisol concentration following ACTH stimulation, which increased during treatment in both groups: 598 nmol/L at baseline and 666 nmol/L at the end of treatment with budesonide/formoterol vs 621 nmol/L at baseline and 635 nmol/L at the end of treatment with budesonide (mean ratio from baseline to end of treatment was 8% higher with budesonide/formoterol compared with budesonide [$p = 0.40$]).

Discussion

In this large-scale, double-blind, 12-month study involving over 1800 patients, we assessed whether a single inhaler containing budesonide/formoterol (Symbicort Turbuhaler) could be used safely and effectively for both maintenance therapy and symptom relief in patients with moderate to severe persistent asthma. Almost half the patients randomised were receiving ICS and a long-acting β_2-agonist at entry and most (83%) patients were classified as having severe asthma[3]. In this patient population, the budesonide/formoterol single inhaler therapy management approach was shown to be as well tolerated as a higher fixed dose of budesonide plus as-needed short-acting β_2-agonist, while providing superior asthma control – significantly reducing the risk of a severe exacerbation by 39% compared with a 2-fold higher dose of budesonide. Budesonide/formoterol single inhaler therapy also reduced nocturnal asthma symptoms, increased asthma-control days and improved lung function compared with a higher dose of budesonide.

The number of severe exacerbations with budesonide/formoterol single inhaler therapy was consistently lower throughout the 12-month study period (Figure 3). The reduction in the risk of severe exacerbations was larger than that observed in previous studies comparing budesonide plus formoterol with a 4-fold higher dose of budesonide in patients with moderate to severe asthma[20], or where salmeterol was added to fluticasone or beclomethasone and compared with a 2-fold higher dose of ICS alone[21]. In the meta-analysis reported by Shrewsbury and co-workers[21], although significantly fewer patients experienced moderate or severe exacerbations with the addition of salmeterol to ICS compared with those receiving a 2-fold higher dose of the ICS, the treatment difference (2.4% of patients) was not clinically important (NNT 41; $p = 0.03$)[21]. Conversely, in the current study the NNT to prevent 1 patient having a severe exacerbation requiring medical intervention per year with budesonide/formoterol vs a higher dose of budesonide alone was 5, suggesting that budesonide/formoterol single inhaler therapy can markedly improve exacerbation control.

Budesonide/formoterol single inhaler therapy improved daily asthma control, with 31 more asthma-control days/patient-year and 12 fewer nights with awakenings/patient-year than a higher dose of budesonide. The improved daily control was reflected by a sustained improvement in lung function and sustained reduction in as-needed medication use throughout the 12-month study compared with budesonide. The improved efficacy provided by this complete asthma management approach in a single inhaler was achieved with a mean budesonide intake of 466 µg/day compared with 640 µg/day in the budesonide group. Furthermore, systemic steroid treatment days were reduced with budesonide/formoterol single inhaler therapy compared with budesonide (1776 days vs 3177 days, respectively). Despite the majority of patients having severe asthma at study entry, budesonide/formoterol single inhaler therapy achieved optimal symptom control on 60% of days with a once-daily dosing regimen, without the need for additional as-needed inhalations.

The findings from this study in patients with moderate to severe asthma are in agreement with those from the study by Rabe *et al.*[16] in patients with mild to moderate asthma. The number of severe exacerbations resulting in hospitalisation was reduced by the ratio of 10:1 in favour of budesonide/formoterol plus additional inhalations as needed compared with a higher daily dose of budesonide[16]. Patients in this study used an average of 3 inhalations in total per day – 2 regular maintenance

inhalations plus 1.04 as-needed inhalations[16]. Other studies have also shown that adjusting the maintenance dose of budesonide/formoterol in response to symptoms as directed by a written action plan significantly reduced severe exacerbations compared with fixed dosing with either budesonide/formoterol[4,5] or salmeterol/fluticasone[6]. In contrast, a recent study in patients receiving > 700 µg/day ICS[22] has confirmed that delayed adjustments in ICS alone in response to a pre-defined fall in PEF at the peak of an exacerbation had little effect on preventing or ameliorating severe exacerbations. Thus, earlier and simultaneous adjustment of both monocomponents of the budesonide/formoterol combination may offer advantages in preventing exacerbations compared with adjusting the dose of ICS alone.

The budesonide/formoterol single inhaler therapy approach used in this study and by Rabe *et al.*[16] is differentiated from the adjustable maintenance dosing approach[4-6] because it achieves a more timely adjustment in both budesonide and formoterol therapy in relation to the onset of symptoms, without the need for patients to follow a complex written action plan. Using budesonide/formoterol in this way replaces as-needed short-acting bronchodilator therapy (used to treat routine symptoms) with a more effective treatment that provides immediate symptom relief and additional anti-inflammatory therapy, thus preventing symptoms from developing into exacerbations. Both anti-inflammatory and long-acting bronchodilator medications are delivered with every inhalation of budesonide/formoterol single inhaler therapy. This simplifies treatment because, unlike the adjustable maintenance dosing approach, there is no need for multiple inhalers or a complex action plan. Studies have shown that asthma symptoms and the subsequent use of a short-acting β_2-agonist for symptom relief increase at least 1 week before a full-blown exacerbation[23,24]. Thus, the increased dose and frequency of dosing with anti-inflammatory therapy in response to the first sign of asthma symptoms will coincide with the start of any potential exacerbation when using the budesonide/formoterol single inhaler therapy approach. Evidence suggests that increasing the dosing frequency of budesonide may be at least as important as increasing the total daily dose during periods of poor asthma control[25]. Findings from another study showed that an early increase in the dose and dosing frequency of budesonide in a 7-day burst, at the onset of asthma worsening, reduced the need for treatment with systemic steroids and was as effective as a regular 4-fold higher maintenance dose of budesonide over 6 months[26].

While this study confirms that budesonide/formoterol single inhaler therapy provides more effective asthma control compared with traditional asthma therapy with a higher dose of budesonide, we can only speculate on the mechanisms behind this. Only the single inhaler therapy group received formoterol. Consequently, the exact contribution of the regular maintenance dose of formoterol versus the contribution of the as-needed adjustments in the formoterol or budesonide dose in improving asthma control cannot be determined with the current study design. Previous studies, such as the FACET study[20], demonstrated that the use of maintenance formoterol improves daily asthma control compared with a 4-fold higher budesonide dose, while affecting the rate of severe exacerbations to a lesser extent than the higher dose of budesonide. Furthermore, the use of as-needed formoterol in patients receiving maintenance therapy with a high dose of budesonide has been reported to reduce severe exacerbations, although significant benefit was observed only when severe exacerbations defined by PEF falls were included in the analysis and while maintaining the budesonide dose at a high level in all groups[27]. It is reassuring that the present study showed that all types of exacerbations and all other aspects of asthma control were markedly improved in patients receiving budesonide/formoterol single inhaler therapy, including a 45% reduced rate of severe exacerbations requiring medical intervention, despite an overall reduction in regular budesonide therapy.

The potential of budesonide/formoterol to be used for both maintenance and relief of symptoms is unique to this combination inhaler because of the properties of the monocomponents. The onset of efficacy of budesonide/formoterol appears to be as rapid as salbutamol in both patients with stable asthma with methacholine-induced bronchoconstriction[28] and patients requiring medical attention with acute severe asthma[14]. The dose–response properties of budesonide[20,29] and formoterol[10,30] in improving asthma control and lung function mean that additional doses of budesonide/formoterol can be taken as needed to regain control of asthma. Budesonide/formoterol at occasional doses up to 1920/54 µg[31] and at regular doses of 1280/36 µg/day for 6 months[32] is well tolerated and effective, supporting the use of budesonide/formoterol as both maintenance and reliever medication.

In the present study, the incidence of adverse events related to ICS or β_2-agonist class effects was similar in both treatment groups, suggesting that budesonide/formoterol has a favourable tolerability profile when used for both maintenance and relief in patients with moderate to severe asthma. Moreover, despite the high proportion of patients with severe asthma in the current study, no significant overuse of as-needed medication occurred. Reassuringly, patients receiving budesonide/formoterol used on average only 2.9 inhalations per day – 2 regular daily inhalations plus 0.90 additional inhalations/day as needed[16]. Furthermore, while there was the potential to

receive increased doses of formoterol in the budesonide/formoterol single inhaler therapy group, there was little evidence of this. As-needed use exceeded 2 or 4 inhalations/day on twice as many days in the budesonide plus as-needed terbutaline group compared with the budesonide/formoterol single inhaler therapy group.

A remaining concern related to the use of long-acting β_2-agonists as a reliever is that – because they are so effective in reducing asthma symptoms – they may mask airway inflammation, causing an increase in the ICS dose in the lead-up to an attack to be delayed. This would result in undertreatment of airway inflammation, increasing the risk of severe or difficult-to-treat exacerbations. However, in a recent large study involving 18 000 patients where as-needed formoterol was compared with salbutamol as needed, formoterol was found to reduce severe exacerbations of all types, including hospitalisations[15]. An advantage of the budesonide/formoterol single inhaler therapy approach is that undertreatment with ICS is less of an issue because ICS is delivered with each as-needed inhalation, therefore treating the underlying inflammation. In the present study, exacerbations of all types were markedly reduced with budesonide/formoterol single inhaler therapy and the profiles of asthma symptoms, reliever-medication use and lung function during exacerbations were similar or improved compared with a higher dose of budesonide – possibly indicating that no masking of inflammation was evident in patients receiving budesonide/formoterol single inhaler therapy.

The prevention of severe exacerbations and improved exacerbation profile seen in the present study can be regarded as a good surrogate indicator of maintained inflammatory control with budesonide/formoterol single inhaler therapy. Further long-term studies are warranted, however, to confirm whether the overall improved efficacy achieved with this simplified treatment approach also extends to a similar reduction in relevant biomarkers of airway inflammation and remodelling compared with a higher fixed dose of ICS.

In conclusion, we have shown that a novel asthma management concept using budesonide/formoterol in a single inhaler for both maintenance therapy and relief from symptoms is a valid and beneficial strategy for the treatment of moderate to severe asthma – and could represent a potential advance in asthma treatment, both in terms of increased efficacy and a simplification of the treatment regimen.

Acknowledgement

This study was supported by AstraZeneca, Lund, Sweden.

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CrossRef links are available in the online published version of this paper:
http://www.cmrojournal.com
Paper CMRO-2691, *Accepted for publication*: 28 June 2004
Published Online: 22 July 2004
doi:10.1185/030079904X2051

Respiratory Medicine (2007) 101, 2437–2446

ELSEVIER

RESPIRATORY MEDICINE

Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone ☆

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Received 13 June 2007; accepted 18 July 2007
Available online 1 October 2007

KEYWORDS
Asthma control;
Exacerbations;
Hospitalisations;
Combination therapy;
Maintenance plus as needed

Summary
Background: Budesonide/formoterol maintenance and reliever therapy (Symbicort SMART®) improves asthma control compared with fixed-dose inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) regimens, but its efficacy has not been assessed in comparison with sustained high-dose salmeterol/fluticasone (Seretide™) plus a short-acting β_2-agonist (SABA).
Methods: Patients ($N = 2309$) with symptomatic asthma (aged ≥12 years; forced expiratory volume in 1 s ≥50% predicted), who had experienced an asthma exacerbation in the previous year, were randomised to receive budesonide/formoterol 160/4.5 µg two inhalations twice daily and as needed, or one inhalation of salmeterol/fluticasone 50/500 µg twice daily plus terbutaline as needed, for 6 months.
Results: Time to first severe exacerbation, the pre-specified primary outcome, was not significantly prolonged (risk ratio 0.82; 95% confidence interval 0.63, 1.05). Budesonide/formoterol maintenance and reliever therapy reduced total exacerbations from 31 to 25 events/100 patients/year ($P = 0.039$), and exacerbations requiring hospitalisation/emergency room (ER) treatment from 13 to 9 events/100 patients/year ($P = 0.046$).

☆ *Clinical trial registration:* NCT00242775.

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0954-6111/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.rmed.2007.07.014

The treatments showed no difference in measures of lung function or asthma symptoms. The mean dose of ICS received was lower using budesonide/formoterol maintenance and reliever therapy (792 μg/day budesonide [1238 μg/day beclomethasone dipropionate (BDP) equivalent] versus 1000 μg/day fluticasone [2000 μg/day BDP equivalent] with salmeterol/fluticasone therapy; $P<0.0001$). Both treatments were well tolerated.
Conclusion: In the treatment of uncontrolled asthma, budesonide/formoterol maintenance and reliever therapy reduces the incidence of severe asthma exacerbations and hospitalisation/ER treatment with similar daily symptom control compared with sustained high-dose salmeterol/fluticasone plus SABA. This benefit is achieved with substantially less ICS exposure.

Introduction

The aim of modern asthma management is to improve control of the disease. This is reflected in guidance produced for healthcare professionals with the intention of improving patient care.[1,2] Furthermore, it should provide patients with an effective means of addressing deteriorations in asthma, so that severe exacerbations can be averted.[3–6]

When control of asthma is not achieved in adults using low-dose inhaled corticosteroids (ICS), ICS/long-acting β_2-agonist (LABA) combination therapy is the recommended treatment approach.[6–11] Surveys of asthma, however, have shown that the majority of patients using an ICS/LABA combination or ICS alone still require daily short-acting β_2-agonist (SABA) therapy, with high proportions reporting daytime symptoms, awakenings and hospital admissions due to asthma.[3–5,12]

The challenge of residual symptoms in adults using ICS/LABA combinations can now be managed in two ways. One option is to increase the maintenance dose of the fixed-dose ICS/LABA combination (budesonide/formoterol or salmeterol/fluticasone), with the aim of progressively stabilising the underlying disease process to minimise the need for short-acting reliever therapy.[7,13,14] An alternative, more patient-centred option, is the use of budesonide/formoterol for both maintenance and relief. This approach is possible because the rapid onset of formoterol[15] allows its use for relief, unlike combination products containing the slower-acting bronchodilator, salmeterol.[16]

Use of budesonide/formoterol maintenance and reliever therapy (Symbicort SMART®) relies on rapid as-needed adjustments in ICS/LABA, as opposed to SABA therapy, to fine-tune asthma control. This approach has the advantage over fixed-dose ICS/LABA plus SABA of substantially reducing severe exacerbations.[17–20] This new management approach is now endorsed in the updated Global Initiative for Asthma (GINA) guidelines as an effective treatment strategy for preventing asthma exacerbations and improving asthma control.[6]

In a large, 6-month, double-blind study, treatment with budesonide/formoterol 160/4.5 μg twice daily (bid) plus as needed reduced exacerbation rates by 28–39% compared with either budesonide/formoterol 320/9 μg bid or salmeterol/fluticasone 250/50 μg bid plus SABA as needed.[20] This result was also replicated in a 1-year, open-label, randomised study performed in a clinical setting, mirroring normal treatment practice, which showed that dose titration of salmeterol/fluticasone combination therapy was less effective than budesonide/formoterol maintenance and reliever therapy, with the latter approach reducing the rate of severe asthma exacerbations by 22%.[19] Although the open-label study allowed maintenance doses to be adjusted in line with clinician judgement, only 40% of salmeterol/fluticasone-treated patients were titrated to the highest possible dose (50/500 μg bid), which may have resulted in less than optimal control. In the Gaining Optimal Asthma Control (GOAL) study, across all strata, 68% of patients receiving salmeterol/fluticasone were on the highest dose at the end of treatment.[7] However, as budesonide/formoterol maintenance and reliever therapy has not been tested against sustained high-dose salmeterol/fluticasone therapy, a direct comparison is warranted.

This study assessed the efficacy of budesonide/formoterol 2 × 160/4.5 μg bid plus as needed, compared with salmeterol/fluticasone (50/500 μg bid) plus SABA as needed, in a double-blind setting.

Methods

Study design

This was a 6-month, randomised, double-blind, parallel-group, multinational study (study code D589 0C00002), comprising 184 centres in 17 countries. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by independent ethics committees. Written consent was obtained from all patients, and parents or guardians of adolescents. The first patient was enrolled on 2 May 2005 and the last patient completed the study on 29 May 2006.

Patients visited the clinic at the beginning and end of run-in (visits 1–2), and after 4, 13 and 26 weeks of treatment (visits 3–5). During the 2-week run-in period, patients used their regular maintenance dose of ICS (in combination with a LABA if used as maintenance prior to study entry), plus terbutaline (Bricanyl® Turbuhaler®, AstraZeneca, Sweden) as needed. After run-in, eligible patients were randomised to receive either budesonide/formoterol (Symbicort® Turbuhaler®, AstraZeneca, Sweden) 2 × 160/4.5 μg bid, plus as needed (budesonide/formoterol maintenance and

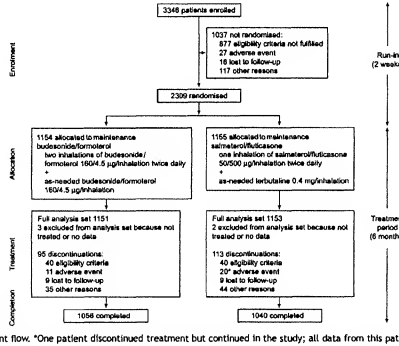

Figure 1 Patient flow. *One patient discontinued treatment but continued in the study; all data from this patient are included in the efficacy analysis in accordance with the full analysis set principle.

reliever therapy), or salmeterol/fluticasone (Seretide™ Diskus™, GlaxoSmithKline, UK) 50/500 µg bid, plus terbutaline 0.4 mg/inhalation for symptom relief (Figure 1). Randomisation codes were sequentially assigned in balanced blocks from a computer-generated list at AstraZeneca R&D, Lund, Sweden. Patients were randomised strictly sequentially as they became eligible. Maintenance and as-needed medication were administered in a blinded double-dummy fashion, with each subject receiving two inhalers for maintenance (one Turbuhaler [red dot], containing budesonide/formoterol or placebo; one Diskus™, containing salmeterol/fluticasone or placebo) and one Turbuhaler® (white) containing budesonide/formoterol or terbutaline for relief.

Study subjects

Outpatients aged 12 years or more, with persistent asthma, who had been treated with ICS alone (800–1600 µg/day) or ICS (400–1000 µg/day) in combination with LABA for at least 3 months prior to study entry, were eligible for inclusion. All eligible patients had a pre-bronchodilator forced expiratory volume in 1 s (FEV_1) ≥ 50% of predicted normal value, with ≥ 12% reversibility following 1.0 mg terbutaline, and had experienced one or more clinically important asthma exacerbations (as judged by the clinician) in the previous 12 months (but none in the month before enrolment). To be eligible for randomisation at the end of run-in, patients had to have used as-needed terbutaline on ≥ 5 of the previous 7 days, with no more than eight inhalations in any single day. Exclusion criteria included recent respiratory infection, use of systemic corticosteroids within 30 days of study entry, use of any β-blocking agent (including eye drops) and a smoking history of ≥ 10 pack-years.

Assessments

The primary outcome was time to first severe exacerbation, defined as deterioration in asthma leading to hospitalisation/emergency room (ER) treatment and/or oral corticosteroid treatment for at least 3 days.[21] Secondary outcomes included the rate of severe exacerbations (as the same composite), the time to first hospitalisation/ER treatment and the rate of hospitalisation/ER treatments.

Measures of daily asthma control, including peak expiratory flow, reliever use, asthma symptoms and nights with awakenings due to asthma symptoms, were recorded by patients in daily asthma diaries. From these assessments, a composite measure of asthma control days (day and night with no asthma symptoms, no awakenings due to asthma symptoms and no use of as-needed medication) was derived. At clinic visits, adherence was checked by investigators, spirometry (FEV_1) was performed and patients completed an Asthma Control Questionnaire (5-item version; ACQ-5), consisting of five questions on symptom control (excluding responses based on FEV_1 and as-needed medication use, which are included in the ACQ-7), each scored on a scale of 0–6, where 0 represents good control and 6 represents poor control. The overall score from the ACQ-5 was the mean of the five responses.

Total use of as-needed inhalations recorded in patient diaries was also used to evaluate the mean daily dose of ICS with budesonide/formoterol maintenance and reliever therapy in delivered budesonide and beclomethasone dipropionate (BDP)-equivalent doses.[4]

Statistical analysis

The primary objective was to compare the time to first severe asthma exacerbation between treatment groups. A total of 985 randomised and evaluable patients per treatment group were required for a log-rank test (at the two-sided 5% significance level) to have a 90% chance of detecting a between-group difference, assuming a true difference of 11% versus 16% in the patients who experienced a severe asthma exacerbation. All patients for whom data were collected after randomisation were included in the full analysis set. Safety analyses were based on all patients taking at least one dose of study medication.

Time to first severe exacerbation was described using Kaplan–Meier curves, and treatment groups were compared using a Cox proportional hazards model, stratified by country, with treatment as a factor. The total number of severe exacerbations was compared between treatment groups using a Poisson regression model with treatment and country as factors, and time in study as an offset variable. The same methods were used to perform an additional *post hoc* analysis comparing differences in exacerbation risk between the two groups in relation to single days with >2, >4, >6 and >8 inhalations of as-needed reliever medication. Other efficacy measures, including spirometry, peak expiratory flow, asthma symptoms, as-needed medication use and ACQ-5 score, were compared between groups as changes from baseline using analysis of variance, with treatment and country as factors and baseline as a covariate.

Results

Patient profile

Of the 3346 patients enrolled, 2309 were randomised and 2304 were included in the full analysis set (see Figure 1 for patient flow). Baseline characteristics were comparable between the two treatment groups (Table 1). Self-reported adherence to maintenance medication was high (mean use was 98% according to patient diary cards in both groups).

Exacerbations

Time to first exacerbation was not significantly different between treatment groups (hazard ratio 0.82; $P = 0.12$). However, Kaplan–Meier plots of time to first and second exacerbation (Figure 2) show that budesonide/formoterol maintenance and reliever therapy tended to prolong the time to the first and repeat exacerbations. This was reflected in a 21% reduction in overall exacerbation rate versus high-dose salmeterol/fluticasone (25 versus 31 events/100 patients/year; $P = 0.039$; Table 2). The risk of a hospitalisation/ER treatment for asthma was also decreased versus high-dose salmeterol/fluticasone plus SABA (hazard ratio 0.64; $P = 0.031$), and a 31% reduction in the rate of hospitalisation/ER treatment was seen with budesonide/formoterol maintenance and reliever therapy (9 versus 13 events/100 patients/year, respectively; $P = 0.046$; Table 2). The 21% reduction in the rate of exacerbations seen with budesonide/formoterol maintenance and reliever therapy compared with high-dose salmeterol/fluticasone was consistent (±1%) for patients pre-exposed or not exposed to LABA at study entry.

Table 1 Baseline characteristics of patients.

Characteristic	Budesonide/formoterol maintenance and reliever therapy ($N = 1154$)	High-dose salmeterol/fluticasone + SABA ($N = 1155$)
Male, *n* (%)	443 (38)	444 (38)
Mean age, years (range)	40 (12–80)	39 (12–80)
Time since diagnosis*, years (range)	14 (1–67)	13 (1–77)
Exacerbations during last 12 months (range)	1.8 (1–10)	1.9 (1–24)
FEV_1, l (range)	2.08 (0.60–4.65)	2.10 (0.72–4.89)
FEV_1, % predicted normal (range)	70.2 (45–114)	71.0 (45–122)
FEV_1 reversibility, % (range)	23.9 (7–103)	23.9 (7–95)
Smoking status		
Never, *n* (%)	949 (82)	952 (82)
Previous, *n* (%)	154 (13)	151 (13)
Smokers, *n* (%)	51 (4)	52 (5)
ICS†use at entry, µg/day delivered dose (range)	705 (250–1600)	720 (200–2000)
Inhaled LABA use at entry, *n* (%)	645 (56)	622 (54)

Data are means unless otherwise indicated; *median value.
SABA = short-acting β_2-agonist.
FEV_1 = forced expiratory volume in 1 s.
ICS = inhaled corticosteroid.
LABA = long-acting β_2-agonist.

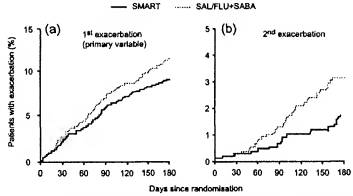

Figure 2 Kaplan–Meier plots of (a) time to first severe asthma exacerbation and (b) time to second severe exacerbation. The risk of a first exacerbation was not different between the treatments with statistical significance ($P = 0.12$). SMART = budesonide/formoterol maintenance and reliever therapy. SAL/FLU+SABA = high-dose salmeterol/fluticasone + short-acting β_2-agonist.

Table 2 Burden of severe asthma exacerbations.

	Treatment group		Reduction in the risk and rate (%) of exacerbations with budesonide/formoterol maintenance and reliever therapy (95% CI); P-value
	Budesonide/formoterol maintenance and reliever therapy ($N = 1157$)	High-dose salmeterol/ fluticasone + SABA ($N = 1153$)	
All patients (intention-to-treat population)			
Severe asthma exacerbations (all definitions)			
Patients with event, *n* (%)	108 (9.4)	130 (11.3)	18[a] (−5, 37); $P = 0.09$[a]
Rate, events/100 patients/year	25	31	26[b] (4, 42); $P = 0.019$[b]
Total number of events[d]	137	173	
ER visits or hospitalisations			
Patients with event, *n* (%)	39 (3.4)	72 (6.2)	46[a] (4, 57); $P = 0.031$[a]
Rate, events/100 patients/year	9	17	31[b] (1, 51); $P = 0.040$[b]
Total events[d]	51	78	
Patient subgroup with use of > 4 inhalations of reliever medication on at least one study day			
Number within subgroup, *n* (%)	305 (26.5)	333 (28.9)	
Severe asthma exacerbations following the first use of > 4 inhalations/day (all definitions)			
Patients with event, *n* (% of subgroup)	46 (15.1)	80 (24.0)	
Rate, events/100 patients/year in subgroup	54	92	41[b] (19, 57); $P = 0.0012$[b]
ER visits or hospitalisations following the first use of > 4 inhalations/day			
Patients with event, *n* (% of subgroup)	17 (5.6)	39 (11.7)	
Rate, events/100 patients/year in subgroup	20	42	53[b] (27, 71); $P = 0.0037$[b]

[a]Treatment comparisons from a Cox proportional hazards model of time to first severe asthma exacerbation.
[b]Comparison of relative rates from a Poisson regression; [c]*a priori* analysis; [f]*post hoc* analysis; [d]descriptive statistics only.

Pattern of reliever use in relation to exacerbations

Days with a high number of as-needed inhalations of > 4, > 6 and > 8 reliever inhalations/day (indicating periods with poorly controlled asthma) occurred with salmeterol/fluticasone plus SABA in 333 (29%), 151 (13%) and 49 (4%) patients, and with budesonide/formoterol maintenance and reliever therapy in 305 (27%), 106 (9%) and 32 (3%) patients, respectively. The incidence of severe exacerbations in association with this pattern of high as-needed use was reduced with budesonide/formoterol maintenance and reliever therapy more than with high-dose salmeterol/fluticasone plus SABA. Kaplan–Meier plots in Figure 3 show the time to first severe exacerbation in the 28-day period after the first day of high reliever use, revealing that, at times of increasingly poor asthma control, budesonide/formoterol maintenance and reliever therapy provided added protection from exacerbations compared with high-dose

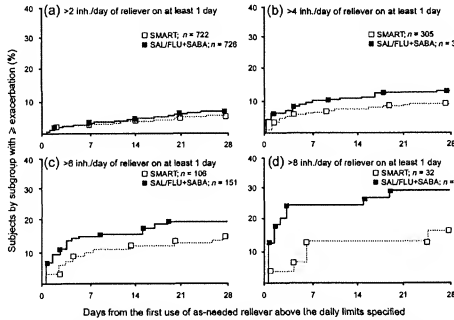

Figure 3 Kaplan–Meier plots showing the percentage of patients with ≥1 exacerbation in the month following the first day with (a) >2, (b) >4, (c) >6 and (d) >8 inhalations/day of as-needed medication. SMART = budesonide/formoterol maintenance and reliever therapy. SAL/FLU + SABA = high-dose salmeterol/fluticasone + short-acting β_2-agonist. inh. = inhalations.

salmeterol/fluticasone plus SABA. The incidence of exacerbations following the first day with >4 inhalations of reliever therapy are shown in Table 2.

Measures of control

Table 3 shows similar improvements in daily symptom control. Asthma control days increased in both treatment groups, from 6.3% and 5.8% at baseline to 44.0% and 44.9% in the budesonide/formoterol and high-dose salmeterol/fluticasone groups, respectively. Similarly, ACQ-5 scores decreased in both groups with no significant difference between groups, indicating similar clinically relevant improvements in asthma control (Table 3).[22]

FEV_1 increased in both groups, from 2.29 to 2.52 l with budesonide/formoterol and from 2.27 to 2.49 l with high-dose salmeterol/fluticasone, with no difference between the treatments.

Study drug use and treatment cost

No as-needed medication use occurred on 59% of days in both treatment groups, although patients used a mean of 0.95 and 1.01 inhalations/day in the budesonide/formoterol and salmeterol/fluticasone groups, respectively. Mean daily doses of ICS were substantially lower in the budesonide/formoterol group than in the high-dose salmeterol/fluticasone group. With salmeterol/fluticasone, the fluticasone dose was fixed at 1000 μg/day (2000 μg BDP equivalent), and in the budesonide/formoterol maintenance and reliever therapy group, the mean budesonide dose was 792 μg/day (1238 μg BDP equivalent), representing an average 38% reduction in BDP-equivalent dose ($P<0.0001$).

There were 764 days of oral steroid use due to exacerbations among 88 (7.6%) of the patients in the budesonide/formoterol group, compared with 990 days among 108 (9.4%) patients in the salmeterol/fluticasone group. This indicates a substantial overall reduction in the necessity for oral steroid use due to exacerbation in the budesonide/formoterol group.

Study drug costs/patient/year were estimated for five countries participating in the study. The reduced drug load was associated with reduced drug costs for budesonide/formoterol maintenance and reliever therapy versus high-dose salmeterol/fluticasone plus SABA, although this benefit varied by country. In four of the five countries assessed (Germany, Spain, Australia and Canada), costs were significantly reduced, by 4%, 5%, 11% and 24%, respectively (all $P<0.001$ versus salmeterol/fluticasone). No decrease in cost was seen with budesonide/formoterol maintenance and reliever therapy in France (1% increase versus salmeterol/fluticasone; $P = 0.10$).

Safety

The number of patients reporting adverse events (39% with budesonide/formoterol, 40% with salmeterol/fluticasone) and serious adverse events (3% with budesonide/formoterol,

Table 3 Mean outcome measures of daily control and ACQ assessed during run-in and on-treatment.

	Treatment group		Treatment comparison (95% CI); P-value[a]
	Budesonide/formoterol maintenance and reliever therapy (N = 1144)	High-dose salmeterol/ fluticasone + SABA (N = 1145)	
Use of as-needed medication			
Total inhalations daily			
Run-in	2.23	2.29	−0.04 (−0.42, 0.04);
On-treatment	0.95	1.01	P = 0.56
As-needed free days, %			
Run-in	10.3	9.3	0.80 (−3.6, 1.9);
On-treatment	58.2	58.4	P = 0.56
Asthma symptoms			
Total symptom score, 0–6 scale			
Run-in	1.87	1.89	0.00 (−0.06, 0.07);
On-treatment	0.98	0.98	P = 0.92
Symptom-free days, %			
Run-in	10.7	11.2	−0.50 (−3.3, 2.3);
On-treatment	47.2	48.1	P = 0.73
Awakenings, %			
Run-in	32.1	32.2	−1.30 (−2.8, 0.3);
On-treatment	12.0	13.3	P = 0.11
Asthma control days, %			
Run-in	6.3	5.8	−1.30 (−4.1, 1.5);
On-treatment	44.0	44.9	P = 0.37
ACQ-5 (0–6 scale)			
Run-in	1.84	1.89	−0.07 (−0.07, 0.04);
On-treatment	1.08	1.12	P = 0.59
PEF (l/min)			
Morning			
Run-in	330.1	329.0	−0.8 (−4.4, 2.8);
On-treatment	359.5	359.4	P = 0.67
Evening			
Run-in	336.7	337.7	1.4 (−2.1, 4.9);
On-treatment	362.3	361.7	P = 0.42

Asthma control day = a day and night with no asthma symptoms, no awakenings due to asthma symptoms and no use of as-needed medication; PEF = peak expiratory flow.
[a]Treatment comparison using an analysis of variance model with country and treatment as factors and run-in included as a covariate.

3% with salmeterol/fluticasone) were similar in both treatment groups. Discontinuations were rare in both treatment groups; there were 31 in total (11 with budesonide/formoterol, 20 with salmeterol/fluticasone). Discontinuations in the salmeterol/fluticasone group included eight reports of events associated with the class effects of ICS or β_2-agonists (dysphonia, oral candidiasis, oral fungal infection, tremor, tachycardia and palpitations), compared with only one such report in the budesonide/formoterol group (headache). One death occurred during the study (in the budesonide/formoterol group; severe typhoid fever) but was not considered by the investigator to be causally related to the study drug.

Discussion

This study compared two highly effective asthma treatment strategies, budesonide/formoterol as maintenance and reliever therapy, and high-dose salmeterol/fluticasone (100/1000 μg/day) supplemented with terbutaline as needed. In both of the study arms, symptoms, lung function and reliever use all improved, and there was not a significant difference in the pre-specified primary outcome, time to first severe exacerbation. There were, however, significantly greater, and clinically important, reductions in the overall number of exacerbations and in exacerbations specified by hospitalisation or ER treatments, by 21% and

31% with budesonide/formoterol maintenance and reliever therapy versus high-dose salmeterol/fluticasone, respectively. The lack of difference between treatments in time to first severe exacerbation, in spite of significant differences in the secondary outcome parameters for severe exacerbations, may be the result of the short duration of the study; increasing the duration to 12 months may have permitted a difference to be observed, as has been seen elsewhere.[19]

In patients randomised to budesonide/formoterol maintenance and reliever therapy, 59% of days were free of any reliever use, which is identical to the percentage of reliever-free days in those subjects randomised to high-dose salmeterol/fluticasone. On these days, patients treated with budesonide/formoterol maintenance and reliever therapy were managed with half the daily dose of ICS used by the salmeterol/fluticasone group, i.e. 1000 μg/day versus 2000 μg/day BDP equivalents. However, overall, patients treated with budesonide/formoterol maintenance and reliever therapy used a mean of 762 μg/day less than those in the salmeterol/fluticasone group. The average reliever use overall was also similar in the two treatment groups, at approximately one dose/day. The number of days of high reliever use was small, and was similar in the two study arms. The absence of overuse and the overall pattern of reliever use replicate findings in other budesonide/formoterol studies. This randomised, blinded study demonstrates that there is no basis to favour the alternative approach of high-dose salmeterol/fluticasone treatment on the grounds that it will improve symptoms and eliminate the inconvenience associated with reliever use.

This study has shown that budesonide/formoterol maintenance and reliever therapy provides an effective intervention during periods of unstable asthma. Days with an increased number of as-needed inhalations (>2, >4, >6 and >8 inhalations/day) were used to identify periods of worsening asthma. The pattern of severe exacerbations following these high-use days revealed that the budesonide/formoterol maintenance and reliever therapy approach provided patients with greater protection from severe exacerbations at times of asthma worsening (Figure 3). The numbers of exacerbations increased more strikingly with the level of as-needed use in the high-dose salmeterol/fluticasone plus SABA group than with budesonide/formoterol maintenance and reliever therapy. In both treatment groups, patients who had used more than four reliever doses on any single day had a higher than average risk for severe exacerbation. However, the proportional reduction in severe exacerbations in those patients using more than four reliever doses per day was greater in the budesonide/formoterol group. In this group the use of salmeterol/fluticasone treatment, rather than budesonide/formoterol maintenance and reliever therapy (Table 2), was associated with more than double the rate of hospitalisations/ER treatments.

This study demonstrates that, despite using moderate to high doses of ICS/LABA in both treatment groups, episodes of high reliever use on a single day are still common and can often be associated with a high risk of imminent exacerbation, but that these exacerbations are not inevitable. The most common intervention advised in asthma action plans for such episodes is doubling of ICS, but this often proves ineffective.[21,24] This study has shown that budesonide/formoterol maintenance and reliever therapy, in periods of increased exacerbation risk, increases ICS/LABA doses in line with disease activity, which is associated with clear efficacy benefits.

Taken together, these findings suggest that the greater the exacerbation risk, the greater the benefit of budesonide/formoterol. It is therefore important to educate patients about the importance of using their budesonide/formoterol reliever when asthma symptoms occur.

Reassuringly, despite the substantial reduction in ICS dose with budesonide/formoterol maintenance and reliever therapy, no difference was shown between the two regimens in any aspect of daily symptom control or asthma control assessed by questionnaire. This reflects the observation that both treatment groups had effective asthma treatment, with visible increases in asthma control from run-in. Full clinical control of symptoms (asthma control days) occurred in approximately half of the treatment days in both groups (44–45%); this was nevertheless substantially higher than the 6% of asthma control days at baseline in both groups. Both treatment strategies were equally well tolerated, confirming the favourable safety profiles of the two treatment approaches, as seen in previous studies.[19,20]

The reduction in the rate of exacerbations with budesonide/formoterol maintenance and reliever therapy compared with high-dose salmeterol/fluticasone was consistently observed (range 21–22% reduction), whether patients used ICS alone or ICS plus LABA at study entry. This finding therefore negates the need for a prior trial of ICS/LABA ahead of implementing the budesonide/formoterol maintenance and reliever therapy approach. In addition, the convenience of ICS/LABA combined in one inhaler is increased further when the same inhaler can be used for maintenance and relief. These features, coupled with reduced ICS load and potential savings in treatment costs with budesonide/formoterol maintenance and reliever therapy compared with high-dose salmeterol/fluticasone, should not be overlooked when deciding which treatment approach to utilise.

The exact mechanisms for increased exacerbation control with budesonide/formoterol maintenance and reliever therapy have yet to be fully determined. A detailed discussion of the potential contribution made by budesonide and formoterol is beyond the scope of the present article and readers are referred to a recent review article.[25] However, one important factor, supported by current findings in high as-needed users, is the early increase in anti-inflammatory treatment provided by as-needed inhalations of budesonide/formoterol during periods of deteriorating symptoms. Indeed, use of high-dose budesonide has been shown to reduce eosinophilic inflammation within a 6-h period.[26] Additional non-genomic effects of as-needed budesonide have been reported, including rapid airway vasoconstriction leading to a reduction in airway oedema.[25,27,28] Single doses of budesonide/formoterol have also been shown to provide complete protection from late-phase bronchoconstrictor responses provoked by allergens, an effect not fully obtained with budesonide or formoterol monotherapy.[29]

When considering as-needed formoterol, switching patients from terbutaline to formoterol as needed has been shown to be effective in reducing asthma exacerbations in

patients already using budesonide/formoterol combination therapy.[18] Thus, increasing doses of formoterol in the presence of ICS is associated with increased protection from exacerbations.[18,30] Higher doses are not recommended with salmeterol, a partial β_2-agonist, which has a plateau in its efficacy at around 100 μg/day.[31,32] In a recent systematic review of over 4000 patients, comparing single inhaler combinations containing formoterol or salmeterol at equivalent fixed ICS doses, it was found that exacerbations occur to the same extent with both combinations but fewer result in hospitalisation/ER treatment with budesonide/formoterol compared with salmeterol/fluticasone.[33] Thus, the greater intrinsic efficacy of formoterol may result in it being more effective in protecting patients during periods of increased bronchial challenge compared with salmeterol.[31,34]

Additional beneficial effects on neutrophilic inflammation with formoterol compared with salmeterol have also been shown *in vitro*.[35] Whether these effects play any role in preventing severe exacerbations caused by the viral or bacterial infections that are associated with neutrophilic rather than eosinophilic inflammation is currently uncertain.

A potential limitation of the study is the accuracy level of self-reported medication use. However, a similar pattern of recorded reliever use occurred in both treatment groups, with a rapid reduction in reliever use at the start of study treatment and a further, gradual decline in use during the 6-month treatment period. This pattern of use was consistent with improvement in objective assessments of asthma control at clinic visits, and reported episodic high use of reliever was corroborated by higher rates of exacerbations. Thus, it appears that self-reported use of medication was in line with other treatment outcomes.

The reduced rate of severe exacerbations, including hospitalisations/ER treatments, with budesonide/formoterol maintenance and relief therapy versus high-dose salmeterol/fluticasone confirms the findings of a recent study conducted by Kuna and colleagues, in which budesonide/formoterol 160/4.5 μg bid plus as needed reduced the rate of severe exacerbations by 39% and hospitalisations/ER treatment by 39% compared with salmeterol/fluticasone (100/500 μg daily).[20] The Kuna study was also a double-blind, double-dummy study of 6 months' duration, with similar populations in terms of FEV_1 (percent predicted) and steroid dose at entry. The present study differs in that the design allowed budesonide/formoterol maintenance and reliever therapy to be tested against the maximum approved dose of salmeterol/fluticasone (100/1000 μg daily), which had been used by the majority of patients in the GOAL study when aiming for total control.[7] Our study showed no difference in any measure of daily symptom control between this same maximum dose of salmeterol/fluticasone and budesonide/formoterol maintenance and reliever therapy. The resulting significantly lower severe exacerbation rate seen with budesonide/formoterol maintenance and reliever therapy without any difference in daily asthma control suggests that better overall asthma control may be gained without resorting to up-titration of maintenance medication and increasing exposure to steroids if the budesonide/formoterol maintenance and reliever therapy approach is adopted.

In conclusion, compared with the highest approved dose of salmeterol/fluticasone plus SABA, treatment with budesonide/formoterol as both maintenance and reliever therapy reduces the incidence of severe asthma exacerbations and hospitalisation/ER treatment. Furthermore, this treatment approach provides added protection for patients who still have episodes of deteriorating asthma. Other measures of asthma control were similar in the two treatment groups, but budesonide/formoterol maintenance and reliever therapy is associated with substantially less ICS exposure and is cost effective. These results confirm that budesonide/formoterol maintenance and reliever therapy is the most effective management approach in patients with moderate to severe asthma.

Acknowledgements

We would like to thank the study investigators at each site (Argentina, Australia, Brazil, Canada, China, France, Germany, India, Indonesia, Malaysia, Mexico, the Philippines, Singapore, South Africa, Spain, Thailand and Vietnam) for their work in conducting the trial and Dr. Cindy Macpherson (MediTech Media Ltd., UK) who provided medical writing support on behalf of AstraZeneca. This study was funded by AstraZeneca, Lund, Sweden.

Conflict of interest statement for Professor J. Bousquet:

Professor Bousquet has attended Advisory Boards and given lectures sponsored by AstraZeneca, Altana and GlaxoSmithKline, and has received sponsorship for investigator-generated research from AstraZeneca and GlaxoSmithKline.

Conflict of interest statement for Professor L.-P. Boulet:

Professor Boulet has participated in Advisory Boards for AstraZeneca, Altana, GlaxoSmithKline, Merck Frosst and Novartis in the past 5 years. In this period he has also received lecture fees from 3M, Altana, AstraZeneca, GlaxoSmithKline, Merck Frosst and Novartis, and sponsorship for investigator-generated research from AstraZeneca, GlaxoSmithKline, Merck Frosst and Schering. Additionally, he has research funding for participating in multicentre studies from 3M, Altana, AsthmaTx, AstraZeneca, Boehringer-Ingelheim, Dynavax, Genentech, GlaxoSmithKline, IVAX, MedImmune, Merck Frosst, Novartis, Roche, Schering, Topigen and Wyeth, and support for the production of educational materials from AstraZeneca, GlaxoSmithKline and Merck Frosst.

Conflict of interest statement for Dr. M. Peters:

Dr. Peters has served on Advisory Boards for AstraZeneca and has received honoraria for speaking at meetings from AstraZeneca and GlaxoSmithKline.

Conflict of interest statement for Dr. H. Magnusson:

Professor Magnussen has received grants, honoraria and advisory fees from Boehringer-Ingelheim, AstraZeneca, Altana, Novartis and Chiesi Group within the past 3 years.

Conflict of interest statement for Dr. J. Quirolte:

Dr. Quiralte participated in the AHEAD study as the main investigator for the Allergy Unit of Complejo Hospitalario (Jaen, Spain).

Conflict of interest statement for Dr. N. Martinez-Aguilar: Dr. Martinez-Aguilar has no conflict of interest to declare.

Conflict of interest statement for Dr. Å. Carlsheimer: Dr. Carlsheimer is in full-time employment with AstraZeneca, Sweden.

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CURRENT OPINION

Treat Respir Med 2006; 5 (6): 385-391
1176-3450/06/0006-0385/$39.95/0

Inhaled Glucocorticosteroid and Long-Acting β2-Adrenoceptor Agonist Single-Inhaler Combination for Both Maintenance and Rescue Therapy

A Paradigm Shift in Asthma Management

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Abstract

Despite aggressive fixed-dose (FD) combination therapy with inhaled glucocorticosteroids (ICS) and long acting β2-adrenoceptor agonists (LABA), many patients with asthma remain suboptimally controlled, based on the need for rescue therapy and rates of severe exacerbations. The strategy of adjustable maintenance dosing (AMD) involves adjustment of the maintenance dose, (using a single combination [budesonide/formoterol] inhaler, Symbicort®) in response to variability of asthma control over time. The AMD strategy, like the FD approach, involves the use of a short-acting β2-adrenoceptor agonist (SABA) for rapid relief of bronchospasm. The dose-response characteristics of budesonide/formoterol make the AMD strategy a feasible option that cannot be exploited with the combination of salmeterol/fluticasone propionate (Advair®). Several studies suggest that the AMD strategy is superior to a FD approach in terms of overall asthma control.

Budesonide/formoterol in a single inhaler is as effective as albuterol (salbutamol) for relief of acute asthma episodes, a feature that makes it possible to use this combination for both maintenance and reliever therapy without the need for the use of a SABA. The single-inhaler strategy has been shown to be safe and more efficacious than FD therapy. In particular, the COSMOS study has demonstrated that exacerbation burden is reduced more effectively when the combination (budesonide/formoterol) single inhaler is used for both maintenance and relief compared with FD therapy with salmeterol/fluticasone and albuterol for rescue in patients with moderate-to-severe asthma. These findings suggest that we will have to reconsider our definition of reliever therapy for patients that require long-term therapy with combination ICS and LABA.

The concept of single-inhaler therapy represents a paradigm shift in asthma management that has been validated in several large studies involving thousands of patients. The single-inhaler strategy represents one of the most significant advances in asthma management in many years, and one that appears ideal for adoption in primary care.

Asthma is a chronic inflammatory disease of the airways associated with variable airflow obstruction and symptoms that include cough, wheezing, chest tightness, and shortness of breath.[1] Inhaled glucocorticosteroids (ICS) are considered first-line therapy for suppression of airway inflammation[1,2] and disease stabilization in patients with persistent symptoms. If asthma is not well controlled on low-to-moderate doses of ICS, additional therapy should be initiated; a long-acting β2-adrenoceptor agonist (LABA) should be considered as the add-on therapy of choice.

A combination of LABA and inhaled glucocorticosteroid, in a single inhaler, represents an important advancement in the management of asthma. It has been known for some time[3-7] that in addition to being more convenient than separate inhalers, the combination inhalers achieve asthma control at lower doses of ICS compared with ICS alone. This strategy is also more likely to

prevent patients from over-relying on their reliever medication (e.g. a rapid long- or short-acting β_2-adrenoceptor agonist [SABA]), thereby minimizing the likelihood of ICS under-utilization.

Currently, two combination products – Symbicort® [1] (budesonide/formoterol) and Advair®/Seretide® (fluticasone propionate/salmeterol) – are available in various parts of the world. At present both combination products are utilized using a twice daily maintenance dosage strategy, with a SABA used for relief of asthma symptoms. Given the dose-response characteristics of formoterol[8] and budesonide,[9] the maintenance dose of budesonide/formoterol can be adjusted according to fluctuations in asthma control using a single inhaler. This strategy is known as adjustable maintenance dosage (AMD), and utilizes a SABA as reliever therapy. AMD is not indicated with fluticasone propionate/salmeterol. Recent studies, researching a novel treatment approach where budesonide/formoterol is used as both maintenance and reliever therapy (i.e. where SABA is no longer used as a reliever), suggest that this treatment approach may provide superior asthma control compared with fixed dosage strategies with either budesonide/formoterol or fluticasone propionate/salmeterol. This article reviews the evolution of combination therapy in asthma management and provides an evidence-based perspective on the strategy of single-inhaler therapy consisting of a corticosteroid and a LABA as both maintenance and reliever therapy in individuals with asthma.

1. Comparison of Fixed and Adjustable Maintenance Dose Strategies

Two landmark studies[5,6] utilizing a fixed dose (FD) strategy involving the administration of budesonide and formoterol (using separate inhalers) revealed that this combination was associated with fewer exacerbations compared with a 2- or 4-fold higher dose of ICS. An earlier FD study,[3] which utilized the combination of salmeterol and beclomethasone dipropionate (BDP), was not designed to examine severe exacerbations as a primary endpoint, although salmeterol use was associated with significant improvements in lung function and other indices of asthma control. A prospective, randomized, placebo-controlled study[10] evaluating the influence of salmeterol in combination with ICS (using separate inhalers) on asthma control revealed that exacerbations were not reduced by salmeterol despite improvements in lung function, reliever medication use, and nocturnal awakenings.

The AMD strategy is in keeping with current asthma management guidelines,[1,2] which recommend that after achieving desirable control, asthma medications should be titrated to the lowest dose that maintains control. The AMD regimen allows patients to adjust the maintenance dose of ICS and LABA (in a single inhaler) in response to changes in their level of symptoms – a strategy that employs use of an action plan and ongoing communication between patient and physician. Since both budesonide and formoterol are effective at low doses and exhibit dose-response characteristics over the dose ranges studied clinically,[8,9] this combination is well suited for AMD therapy.

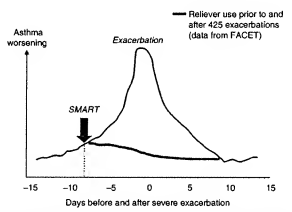

Fig. 1. Reliever use as a function of asthma worsening over time (adapted from Tattersfield et al.,[20] with permission). **FACET** = Formoterol and Corticosteroids Establishing Therapy;[5] **SMART** = Symbicort® Maintenance and Reliever Therapy.

A number of open-label studies[11-13] have helped to clarify the potential benefits of AMD therapy compared with FD therapy. One of the first studies, by Stallberg et al.,[13] revealed that compared with FD (budesonide/formoterol), AMD with budesonide/formoterol reduced exacerbations (6.2% vs 9.5%, $p < 0.05$), reduced daily inhalations of budesonide/formoterol (2.35 vs 3.95, $p < 0.001$), and was associated with lower costs for asthma care over a 6-month period. In a similar study, Fitzgerald et al.[11] reported that AMD with budesonide/formoterol provided more effective asthma control than FD, with a lower overall drug dose and reduced total costs. Aalbers et al.[12] compared budesonide/formoterol (160/4.5μg) AMD versus budesonide/formoterol (160/4.5μg) FD and salmeterol/fluticasone (Seretide® diskus 50/250μg) FD. These authors reported that the odds ratio for achieving a well-controlled asthma week did not differ between groups during the initial 4-week double-blind period, when the FD regimens were utilized. By contrast, during the 6-month open extension period, budesonide/formoterol AMD increased the odds of achieving a well controlled asthma week compared with budesonide/formoterol FD ($p < 0.049$) in association with a 15% reduction in average study drug use. Furthermore, budesonide/formoterol AMD therapy resulted in a lower exacerbation rate over the study period, 40% lower than with salmeterol/fluticasone FD ($p = 0.018$). Other

1 The use of trade names is for product identification purposes only and does not imply endorsement.

studies[14-17] have shown that an AMD strategy may provide similar asthma control compared with a FD strategy at a lower total daily dose. Only one study[18] has shown that FD combination therapy with salmeterol/fluticasone 50/250μg is superior to AMD with budesonide/formoterol. In this study, the majority of patients (82%) on AMD used a minimum of one inhalation once daily, while in the studies described above,[11-13] patients on the AMD strategy used a minimum maintenance treatment of one inhalation twice daily. The results of this study[18] suggest that there is a minimum maintenance dose necessary to prevent deterioration of asthma control.

2. Single-Inhaler Therapy

Despite marked improvement in asthma control reported with the use of combination ICS and LABA therapy,[4,5,7] optimal asthma control is not achieved in many patients based on the requirement for SABA therapy and exacerbation rates. These findings suggest that fluctuations in control represent an inherent feature of the natural history of asthma and may in part be related to inadequate anti-inflammatory therapy. Traditionally, patients have been instructed to increase their SABA use to relieve symptoms. Formoterol, a rapid long-acting bronchodilator, used as a reliever has a similar safety profile to albuterol (salbutamol) and is associated with fewer asthma symptoms and exacerbations than albuterol.[19] Furthermore, budesonide/formoterol in a single inhaler is as effective as albuterol in relieving acute asthma episodes in adults and adolescents.[8] These data have provided important information in the development of the single inhaler concept, a new treatment strategy where budesonide/formoterol is taken as both maintenance and reliever therapy, without the requirement for the use of SABA.

Data from the Tattersfield et al.[20] study suggest that prior to a severe exacerbation (figure 1), there is a period of 5–7 days during which patients experience deteriorating symptoms and lung function. This period represents an opportunity to intervene early with an increase in ICS that is coupled with the rapid acting LABA, formoterol, which has a systemic adverse effect profile similar to a SABA.[21] The recent landmark trial by O'Byrne et al.[22] demonstrated that budesonide/formoterol 80/4.5μg twice daily plus as-needed budesonide/formoterol 80/4.5μg was superior to budesonide/formoterol 80/4.5μg twice daily plus as-needed SABA and to budesonide 320μg twice daily plus as-needed SABA in prolonging the time to first severe exacerbation in adolescents and adults; similar results were seen in children (4–11 years old) given half the maintenance dose once daily at night. This study also demonstrated that single-inhaler therapy with budesonide/formoterol significantly reduced total severe exacerbations requiring medication intervention, and oral corticosteroid use compared with either budesonide/formoterol FD or a 4-fold higher dose of budesonide for maintenance therapy, both using SABA for relief. Of particular interest is the finding that the mean daily dose of budesonide with single-inhaler therapy (240 μg/day for adults and 126 μg/day in children) was less than that in the budesonide plus SABA group (640 μg/day for adults and 320 μg/day in children) despite superior asthma control when budesonide/formoterol single inhaler was used for both maintenance and relief. This finding suggests that it is (in part) the timing of the ICS dose in response to worsening asthma symptoms, rather than the total daily dose of ICS, that determines efficacy. Scicchitano et al.[23] have shown that budesonide/formoterol as maintenance (160/4.5μg, two inhalations once daily) and relief is superior to budesonide maintenance (160μg, two inhalations twice daily) and SABA as relief in prolonging the time to first exacerbation. In this latter study the number needed-to-treat to prevent one severe exacerbation (defined as hospitalization/emergency room treatment or systemic corticosteroid use due to asthma worsening or a fall in the morning peak expiratory flow ≤70% of baseline on two consecutive days) was 5.

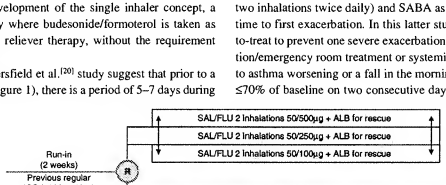

Fig. 2. Study design (reproduced from Vogelmeier et al.,[24] with permission). **ALB** = albuterol (salbutamol); **BUD/FORM** = budesonide/formoterol; **ICS** = inhaled glucocorticosteroid; **LABA** = long-acting β_2-adrenoceptor agonist; **R** = randomization; **SABA** = short-acting β_2-adrenoceptor agonist; **SAL/FLU** = salmeterol/fluticasone propionate.

Table I. Baseline characteristics of patients enrolled in the COSMOS study. Data are presented as mean (range), unless otherwise stated (reproduced from Vogelmeier et al.,[24] with permission)

Characteristic	SAL/FLU + albuterol (salbutamol)	BUD/FORM maintenance + as needed
Patients (no.)	1076	1067
Sex (M/F)	429/647	451/616
Age (y)	45 (12–84)	45 (12–80)
Asthma duration (y)	12 (0–74)	13 (1–75)
FEV_1 pre-terbutaline (% predicted)	73 (28[a]–100[a])	73 (39–115[a])
FEV_1 reversibility (%)	13	13
ICS dose at entry (mg/day)	881 (400[b]–3000)	888 (50[b] –2000)
Baseline ICS medication type (% patients BUD/FLU/BDP)	63/24/13	60/25/15
Inhaled LABA use at study entry [no. of patients (%)]	409 (38)	402 (38)
Reliever use (inhalations/24h)	2.7 (0.3[b]–33.7)	2.6 (0.2[b]–10.7)
Use of ≤4 inhalations of as-needed medication/week (% patients)	5	5
Overall ACQ-5 score	1.87 (0.00–5.00)	1.86 (0.00–5.20)
Overall AQLQ(S) score	4.95 (1.19–7.00)	4.97 (1.75–7.00)

a Mean not adjusted for type of ICS or inhaler choice; minimum doses of ICS stipulated at entry were: BUD 500 µg/day, FLU 500 µg/day, and BDP 1000 µg/day for either metered or delivered doses.

b Deviation from inclusion criteria (included in the intention-to-treat population).

ACQ-5 = Asthma Control Questionnaire 5-item score; **AQLQ(S)** = Asthma Quality of Life Questionnaire (Standardized); **BDP** = beclomethasone dipropionate; **BUD** = budesonide; **FLU** = fluticasone propionate; **FORM** = formoterol; **ICS** = inhaled corticosteroid; **LABA** = long-acting β_2-agonist; **SAL** = salmeterol.

These studies [22,23] underscore the potential to utilize a simple and practical asthma management approach that is associated with a high level of efficacy in patients with moderate-to-severe asthma. These studies also suggest that rescue therapy with budesonide/formoterol may be associated with more rapid stabilization of control during periods of asthma worsening. It is important to note that single-inhaler therapy is also referred to as 'Symbicort® Maintenance and Reliever Therapy' (SMART). [23] It is not known whether this strategy is effective in all patients with asthma, including non-compliant patients and individuals who are bad perceivers of asthma control.

3. The COSMOS Study

3.1 Study Design

The COSMOS Trial[24] represents the first attempt to compare the single inhaler strategy versus a FD strategy utilizing a real-life study design. This 12-month randomized, parallel group, open-label, dose titration study compared the effectiveness and safety of budesonide/formoterol for maintenance plus relief to a FD strategy using salmeterol/fluticasone for maintenance plus salbutamol for relief. A total of 2143 patients with moderate-to-severe symptomatic asthma (mean FEV_1 73% predicted, mean ICS 884 µg/day) were studied (table I). During a 2-week run-in period, patients used their existing ICS (and LABA, if appropriate) and as-needed reliever medication. Thereafter, patients were randomized to treatment with either budesonide/formoterol 160/4.5µg two inhalations twice daily plus additional inhalations for relief of asthma symptoms (single-inhaler therapy) or salmeterol/fluticasone 50/250µg twice daily plus albuterol as a reliever. The maintenance doses (moderate) for each combination were chosen to reflect recommendations in current guidelines.[1,2] After 4 weeks of therapy, asthma control was assessed in both groups by physicians at a scheduled study visit, and onwards either at a scheduled clinic visit or an unscheduled contact. In keeping with routine clinical practice, maintenance therapy in both groups was titrated up or down to improve control or to maintain asthma control at the lowest effective dose (figure 2). Furthermore, patients were not required to keep daily diary cards, and reversibility of airflow obstruction was not a requirement for inclusion (a strategy that would tend to avoid selecting patients more likely to respond to increases in LABA therapy).[25] Finally, titration of maintenance medication was left to physicians' judgment and was not protocol driven.

Patients reported maintenance and reliever medication use during the preceding 2 weeks of each clinic visit; total ICS dose was calculated from the prescribed maintenance dose and self-reported reliever medication use (only for the budesonide/formoterol

group). Scheduled visits were infrequent, to mimic real life clinical practice. Other assessments included measurement of FEV_1, Asthma Quality of Life Questionnaire, and Asthma Control Questionnaire 5-item version.

3.2 Primary Endpoint

The primary endpoint was the time to first severe exacerbation defined as a deterioration in asthma resulting in hospitalization/emergency room (ER) treatment, oral corticosteroids for ≥3 days or an unscheduled visit (patient-initiated) leading to treatment change. Severe exacerbations excluding unscheduled patient-initiated visits not resulting in hospitalization/ER treatment or oral corticosteroid therapy as well as hospitalization/ER treatment alone were analyzed on an *a priori* basis.

3.3 Results and Discussion

Single-inhaler therapy with budesonide/formoterol reduced the risk of a severe exacerbation by 25% ($p = 0.008$), or 23% when unscheduled clinic visits were excluded ($p = 0.025$) compared with salmeterol/fluticasone. The time to first exacerbation was prolonged with the single-inhaler strategy ($p = 0.005$), even when unscheduled clinic visits were excluded ($p = 0.017$). The total rate of severe exacerbations was reduced by 22% with the single-inhaler therapy ($p = 0.0025$; figure 3). Single-inhaler therapy with budesonide/formoterol was associated with 38% less reliever medication use than salmeterol/fluticasone ($p < 0.001$). The mean number of prescribed inhalers per patient per year was 12.7 in the single-inhaler group compared with 16.6 in the salmeterol/fluticasone group.

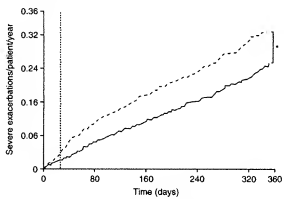

Fig. 3. Cumulative rate plot of time to first and repeat severe asthma exacerbation in both treatment groups (dashed line indicates salmeterol/fluticasone propionate and albuterol [salbutamol] for rescue; solid line indicates budesonide/formoterol maintenance and as needed). The vertical dotted line marks the start of the dose-titration phase (reproduced from Vogelmeier et al.,[24] with permission). * $p = 0.0025$ (Poisson regression analysis of the rate of exacerbations).

A small statistically significant difference in post-bronchodilator FEV_1 was noted in favor of patients in the single-inhaler group (budesonide/formoterol). Health-related quality of life improved from baseline in both groups but there was no statistically significant difference between groups.[24] In both groups, patients used a similar mean total daily dose of budesonide or fluticasone propionate, averaged over the entire treatment period: 562μg (maintenance) + 91μg (for relief of symptoms) for budesonide/formoterol patients versus 583μg (maintenance only) for salmeterol/fluticasone propionate patients. Expressed as equivalent BDP doses, the corresponding values for budesonide/formoterol and salmeterol/fluticasone propionate were 1019 μg/day (maintenance and relief) and 1166 μg/day (maintenance only), respectively. In patients with high reliever use (>4 inhalations/day) the mean total daily dose of ICS was budesonide 910 μg/day (BDP equivalent 1420 μg/day) versus fluticasone propionate 701 μg/day (BDP equivalent 1402 μg/day). Throughout the study, the majority of patients (55%) in the salmeterol/fluticasone propionate group used two different strengths of maintenance inhaler plus albuterol inhaler compared with a single inhaler (of the same strength) for both maintenance and reliever therapy in the budesonide/formoterol group. Single-inhaler therapy with budesonide/formoterol was associated with fewer oral corticosteroid days (≈1000 fewer) and hospital days (35 fewer) compared with salmeterol/fluticasone propionate. In both groups, most patients (76% vs 66% for the budesonide/formoterol and salmeterol/fluticasone propionate groups, respectively) used a maximum of four inhalations per week for relief of symptoms, at study completion. The cost of medication was comparable between the two groups. Both treatments were well tolerated with no notable differences between the groups in number or severity of adverse events.

The use of an open-label design[24] permitted an evaluation of how the single-inhaler concept compared with the FD strategy with salmeterol/fluticasone propionate; the latter potentially requiring three separate maintenance inhalers for dose titration and an additional inhaler for the relief of asthma symptoms.

The use of a single inhaler (budesonide/formoterol) for both maintenance and reliever therapy represents a significant paradigm shift in asthma management that is simple and effective. These features make this strategy particularly appealing for adoption in primary care. The use of a single inhaler for both maintenance and reliever therapy appears to fit well with normal patient behavior, which includes the use of more reliever medication when asthma control declines. When used for symptom relief, the inhaler – which contains an ICS and a rapid acting LABA – both provide relief of acute bronchospasm and eliminates the possibili-

ty of delayed ICS adjustments during periods of asthma deterioration. Interestingly, the study by Woude et al.[26] suggests that during methacholine-provoked bronchoconstriction, budesonide/formoterol induces bronchodilation that is more rapid in onset than with salmeterol/fluticasone, resulting in a significantly greater reduction in dyspnea with budesonide/formoterol.

The benefits observed with the single-inhaler strategy were achieved using a low-to-moderate daily maintenance dose of ICS, in keeping with current guidelines.[1,2] These findings are reassuring and suggest that this simplified treatment approach is unlikely to result in the overuse of medication in clinical practice. Further studies are required to determine how patient adherence is influenced by this novel strategy.

Since dose titration in this study was physician- and not protocol-driven, there is the risk of under-treatment – particularly in the salmeterol/fluticasone propionate group, where patients used only albuterol for rescue. However, asthma control in the salmeterol/fluticasone propionate group improved to a similar level reported in a recent study[7] involving patients receiving salmeterol/fluticasone 100/500 µg/day with upwards protocol-driven dose titration (without downward titration).

Further studies are required to determine how this single-inhaler therapy strategy influences asthma control among patients whose disease is of a more mild form. Given the moderate-to-severe nature of the patients studied in the COSMOS study, direct application to patients with less severe disease is not ideal. However, the report of Rabe et al.[27] suggests that budesonide/formoterol single-inhaler therapy is effective in patients with mild-to-moderate asthma. The findings of the COSMOS study[24] are consistent with the favorable efficacy and safety profiles of budesonide/formoterol maintenance and reliever therapy reported in several double-blind studies including more than 5000 patients,[22,23,26] and serve to validate the effectiveness of this new and simplified asthma treatment strategy.

4. Summary and Conclusions

The COSMOS study[24] clearly demonstrates that exacerbation burden is reduced more effectively when the budesonide/formoterol (single inhaler) combination is used for both maintenance and relief compared with FD therapy with salmeterol/fluticasone propionate and albuterol for rescue. The effectiveness of this strategy suggests that we will have to reconsider our definition of reliever therapy for patients who require long-term therapy with combination ICS and LABA medication. While the simplicity of this strategy appears almost too good to be true, its effectiveness and safety have been confirmed in several large studies involving thousands of patients.

To date the independent and/or complementary benefits of budesonide and formoterol with single-inhaler therapy have not been well described. Studies examining the short-term effects of ICS in asthma suggest that lung function may improve within 6 hours of administration of a single dose.[28,29] Gibson et al.[30] have shown that sputum eosinophil levels were significantly lower compared with placebo 6 hours after a single dose of budesonide, a finding that was also associated with a 2.2-fold improvement in airway responsiveness. Furthermore, the data from Spoelstra et al.[31] indicate that both budesonide and formoterol inhibit cytokine-induced adhesion molecule expression on human lung fibroblasts. Finally, Usmani et al.[32] have reported that combination therapy with fluticasone propionate and salmeterol augmented the action of fluticasone propionate on glucocorticoid receptor nuclear localization. Further studies are required to elucidate more precisely how the individual components of the single-inhaler strategy influence asthma control via independent and/or complementary pathways. The concept of single-inhaler maintenance and reliever therapy represents one of the most important advances in asthma management in many years, and one that appears particularly well suited for utilization in the primary care setting.

Acknowledgments

I would like to acknowledge Deborah K. D'Urzo for her assistance in preparing the manuscript. No sources of funding were used to assist in the preparation of this article, and the author has no conflicts of interest that are directly relevant to the content.

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